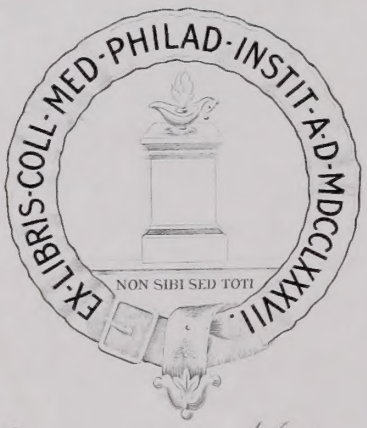
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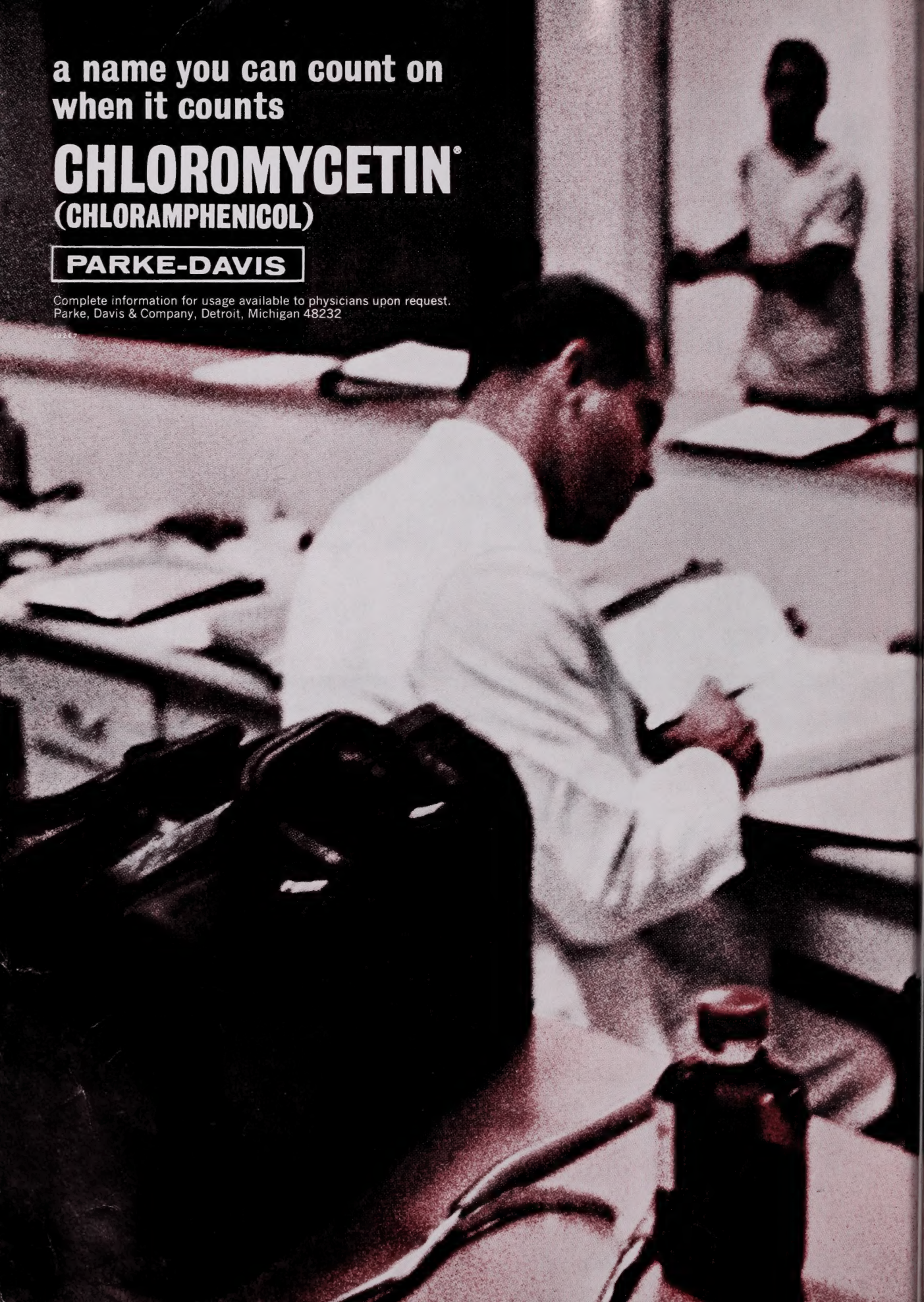
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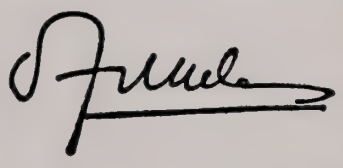


President's Letter

THE TIME has come again for a changing of the guard, though the mainstream of medicine goes on with little regard for these minor surface alterations. Nonetheless, we should commend Doctor Sheppard for his stewardship in the last year, with the full knowledge that his participation and contributions will continue. We should hail also the Council of the State Medical Association and its able chairman, Doctor Sather. These physicians have given generously of their time in shaping the destiny of our Association. Finally, let us salute Mr. Brunn and his staff, newly ensconced in shiny quarters, a fitting environment for these competent and dedicated assistants.

Medicine is never without its problems, and these are likely to be highlighted in an election year. Throughout the forthcoming months, it is hoped that we can explore these areas with the advice and assistance of the splinter societies which come under the state organization umbrella. In such event, this President's page will feature officers of these societies.

On behalf of the Minnesota State Medical Association, its Council and Officers, and the Executive Secretary and Staff, I offer greetings in this new year. May it be prosperous, healthy and interesting!



O. L. N. Nelson, M.D.
President
Minnesota State Medical Association

Food for Thought (radio commentary): A few make things happen; a slightly greater number watch things happen; the large majority is unaware that anything is happening. Does this apply to our medical community?

Little did we guess that what has been called "The Century of the Common Man" would witness as its outstanding feature more common men killing each other with greater facilities than any other five centuries put together in the history of the world.—Winston Churchill, 1949

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Artificial Heart

I—Application of Nonpulsatile Force-Vortex Principle

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EFFORTS AT DEVELOPING a suitable pump for use in constructing an artificial heart have led to the evolution of many novel devices. As yet no device has exhibited sufficient all around performance to permit it to serve as a satisfactory heart substitute. Failures can be attributed basically to two inherent problems common to all devices currently under study: the inefficiency of the units and destruction of blood elements. The former deficiency seems to have presented the more formidable obstacle.

Practically all efforts to date have centered on a study of pumps producing a pulsatile type of flow. Selection of such pumps seems to have been predicated on reasoning that it would be wise to duplicate the normal physiological state (pulsatile flow), and that such units seem to lend themselves to design features by which blood destruction can more readily be prevented.

Nonpulsatile pumps have been described as the ideal heart substitute from the engineering point of view because they possess hydrodynamic characteristics analogous to the mammalian heart.[5] Such pumps do not contain valves; the advantage related to this characteristic has been recognized.[1-4] In addition, they are the most efficient type pump known. Despite these advantages such pumps have been almost universally ignored and apparently no serious efforts have been made to utilize them as artificial heart pumps. This unpopularity has stemmed from the fact that such units have had the characteristic of producing high shear and turbulence and, when tested, have produced a "Waring Blender effect" with marked destruction of the formed elements of the blood.[5] It occurred to us that, since in all other respects such pumps were potentially ideal for use as artificial hearts, attention should be focused on overcoming this single drawback. We felt that with imag-

*Veterans Administration Hospital, Houston, Texas.
**Veterans Administration Hospital, Syracuse, New York.

inative design conception this problem could be surmounted.

With this view in mind we designed, constructed, and tested a nonpulsatile pump. Results of tests carried out on this prototype are described herein. The findings indicate that the objectives have been met in fashioning a pump which retains the desirable engineering features of a nonpulsatile pump while at the same time possessing the capability to circulate blood atraumatically.

Description

The nonpulsatile pump tested operates on the principle of force-vortex or rigid-body motion. For force-vortex motion the tangential velocity is $v_\theta = \omega r$ where ω is the angular velocity and r is equal to the radius. Substitution in the differential equation for pressure gives

$$dp = \rho\omega^2 r dr - \rho g dz$$

where p = pressure, ρ = density, g = gravitational acceleration, and z = elevation.

The pressure difference between any two points in the fluid is

$$p_2 - p_1 = \rho\omega^2 (r_2^2 - r_1^2)/2 - \rho g (z_2 - z_1)$$

where r_1 and r_2 = the radial distances from the center of rotation to points 1 and 2 respectively

p_1 and p_2 = the pressures at points 1 and 2 respectively

z_1 and z_2 = the elevations at points 1 and 2 respectively (3)

In the pump tested, the fluid was constrained from taking the shape of a paraboloid of revolution by the rigid rotator. Therefore, the pressure difference is

$$p_2 - p_1 = \rho\omega^2 (r_2^2 - r_1^2)/2$$

where p_2 = outlet pressure

p_1 = inlet pressure

r_2 = outer radius of rotator

r_1 = inlet radius

This principle of pumping was selected because it offered the least amount of impact on the blood to obtain the pressures and flow rates necessary. The pressures and flow rates were

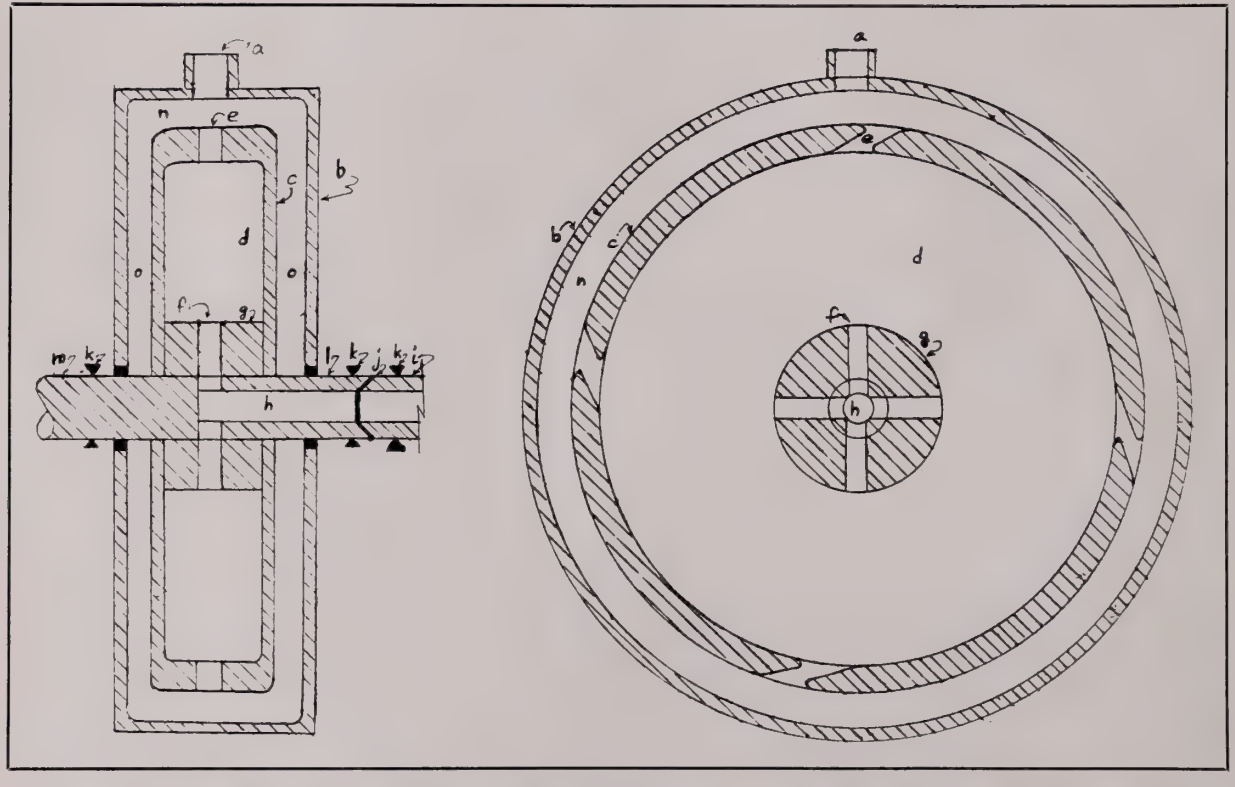


Fig. 1—Schematic cross-sections of artificial heart: (a)—pump outlet, (b)—pump housing, (c)—rotator, (d)—rotator chamber, (e)—rotator outlet, (f)—rotator inlet, (g)—shaft-to-rotator connector, (h)—pump inlet, (i)—stationary teflon inlet, (j)—teflon-to-teflon seal, (k)—bearings, (l)—rotating inlet shaft, (m)—stainless steel pump shaft, (n)—head space, (o)—side space. Plexiglass was used as the construction material for a, b, c, and g. Dimensions: External diameter, rotator, 8½″; External width, rotator, 1¾″; Internal diameter, pump housing, 11⅛″; Internal width, pump housing, 3¼″; Internal diameter, teflon inlet, ½″; Internal diameter, pump outlet, ½″; Outlet and inlet diameters, rotator, ⅜″.

obtained from this principle by imparting a revolutionary motion to the fluid through contact with the rotator walls. The particles of fluid in contact with the rotator walls have imparted on them, due to shear forces, an acceleration. Again, due to shear forces between fluid particles, these particles in turn exert a similar acceleration and force on their neighboring particles. Therefore, in essence, once the initial fluid particles have been accelerated, the rest of the fluid rotates through contact with other fluid particles. Hence, after this initial acceleration the fluid itself (rather than an impeller) becomes the prime mover. This action results in very gentle handling of the fluid.

Figure 1 schematically shows in cross sections the design features of the pump.

Methodology

The pump was subjected to *in-vitro* studies with water, saline, and blood each separately used as the circulating fluid. Performance was then measured by determining pressure head developed, volume output, and efficiency at r.p.m. between 425 and 820. Pooled citrated dogs' blood was used to prime the unit after the internal chambers of the pump were siliconized. The blood was then continuously circulated by the pump through a semi-closed system (Figure 2) for 3½ hours. Temperatures were kept normothermic by producing the proper friction on the bearing surrounding the input port. Serial hematocrit and plasma hemoglobin determinations were done at the beginning and hourly after institution of circulation. Red blood count, white blood count, and platelet determinations were done prior to commencement of and at the conclusion of the period of circulation. Blood samples were collected from the reservoir. Clotting time, clot retraction, and fibrin studies were performed at the conclusion of the experiments. R.p.m.s were measured by means of a stroboscope. In addition, stroboscopic analysis was utilized to study characteristics of fluid flow with water and saline.

Pump efficiency determinations were made by using a calibrated motor to determine input power to the pump at various r.p.m.s, and pressure and flow readings were taken to determine hydraulic power.

Results

Pump efficiencies in the order of 45% were attained.

Figure 3 depicts flow rates achieved against various heads of pressure with water as the circulating fluid with an input pressure of zero. Approximately doubling the r.p.m.s resulted in a 2-to-4 fold increase in flow rate depending on the given peripheral resistance. Essentially similar patterns were obtained when either saline or blood was used as the circulating fluid at a given r.p.m.

During the test periods there was no increase in plasma hemoglobin. No change was detected in the red blood count, white blood count, or hematocrit. Platelets were normal in appearance and numbers at the conclusion of the period of circulation. No defibrinization took place. Neutralization of the citrate effect on the blood with calcium chloride at the conclusion of the tests resulted in prompt clotting of the blood (2½ minutes). Clot retraction in quality and time was normal from blood samples collected at the end of the experiment.

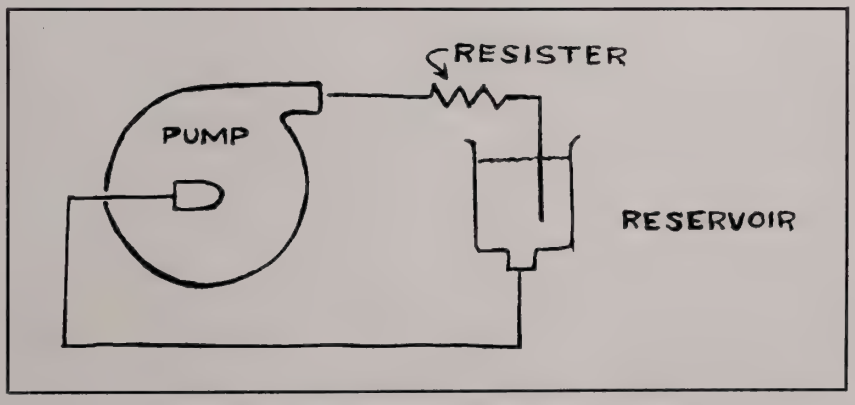


Fig. 2—Schematic diagram of semi-closed system.

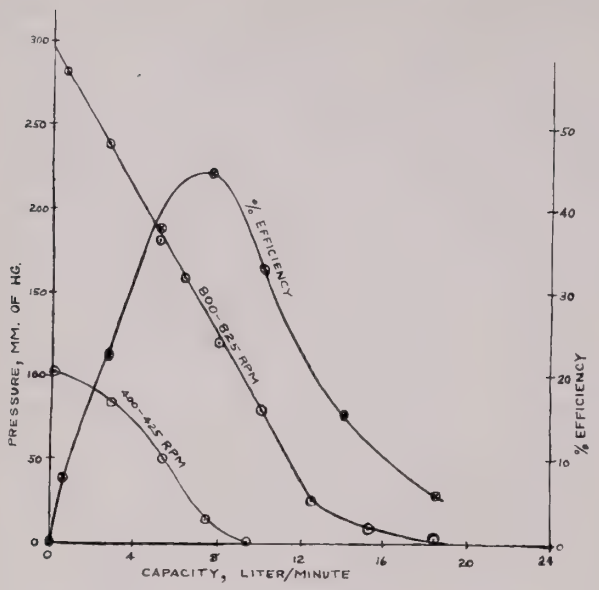


Fig. 3—Capacity vs. pressure and % efficiency.

Discussion

The nonpulsatile pump described exhibits high performance characteristics from the standpoint of efficiency (on the order of 45%) and ability to pump blood without detectable damage.

The prototype which was constructed for these experiments represented only a very crude device fashioned from available "odds and ends." It was fabricated with the sole purpose of establishing the validity of the pumping principle involved. Higher efficiencies should be attainable in more refined models. Streamlining the design, based on data gathered from prototype studies, and careful selection of compatible construction materials should extend the already very impressive blood tolerance characteristics of the pump.

Optimization will involve studies as to the most desirable rotator configuration. Figure 4 depicts three alternate rotator designs immediately under study as possible configurations to supplant disc-shaped rotators. Figure 5 schematically illustrates what we feel may ultimately constitute the optimum mechanical design of this pump. The most desirable number of rotators and their spacing in a given pump have yet to be determined. In the experimental model, for sake of convenience of construction, the inner walls of the housing were stationary; engineering principles suggest that if rotary motion were imparted in the same direction as the rotators to those portions of the pump, it would enhance efficiency and reduce turbulence and shear even further. An even more attractive approach currently under study by our group would be to eliminate the head and side space portion of the pump altogether. Because of the nature of this pump the head and side space can be eliminated in order to achieve

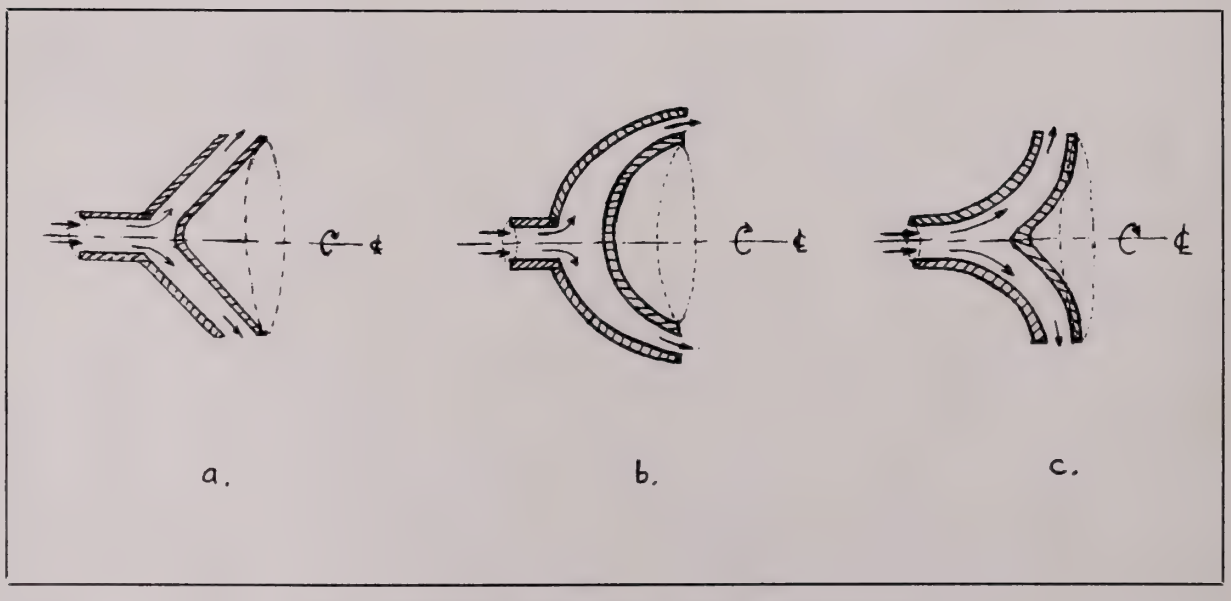


Fig. 4—Schematic Cross-Sections of Three Types of Rotators.

a more compact unit. Studies have been carried out in our laboratory in connection with the staging of such pumps. It has been found that it is possible in this fashion to trade off r.p.m.s for stages to reduce the former to the desired speed. The effect is to lengthen the device at the expense of width. Calculations indicate that a very compact unit can be constructed in this manner and yet obtain the pressure heads and flow rates desired.

The physiological necessity of pulsatile flow is still a moot question.[1,2] From studies we have done it appears possible to easily convert a nonpulsatile to a pulsatile type flow. Thus, should the latter type flow in the future be found to be physiologically necessary, the present type pumping unit is readily adaptable to such conversion. In the meantime, this pump provides an ideal model for use in the study of nonpulsatile flow in both *in-vitro* and *in-vivo* experiments. It should also find application as an atraumatic, efficient heart-lung machine pump.

It is worthy of mention that the only animals available at the time these experiments were carried out were unfasted sick dogs suffering from distemper and heart-worm infestations. Use of blood from these animals we feel resulted in a more critical test of the pump's ability to handle blood atraumatically.

Our observations are in accord with those of Saxton and Andrews,[5] namely, that such pumps as these are auto-regulatory according to physiological requirements, and with right and left heart units operating simultaneously would automatically maintain balanced flows between the two sides. In the nonpulsatile pump they tested (a centrifugal pump) they noted a marked decrease in output when blood was substituted for saline. We found in our pump that there was essentially no difference in flow rates or pressure heads developed, whether water, saline, or blood was used as the circulating fluid.

We agree with the contention of Saxton and Andrews that these type pumps embody qualities which make them potentially ideal artificial heart pumps.[5] However, they found the particular unit which they tested caused marked destruction of the formed elements of the blood. We feel they got the "Waring Blender effect" they noted because, in essence, they used a "Waring Blender." We postulate that the drop in efficiency and output they experienced on using blood was due to the "Waring-Blender effect" causing cavitation of this fluid because of the dissolved gases. The cavitation undoubtedly also contributed to the hemolysis.

Conclusions

A nonpulsatile pump is described embodying

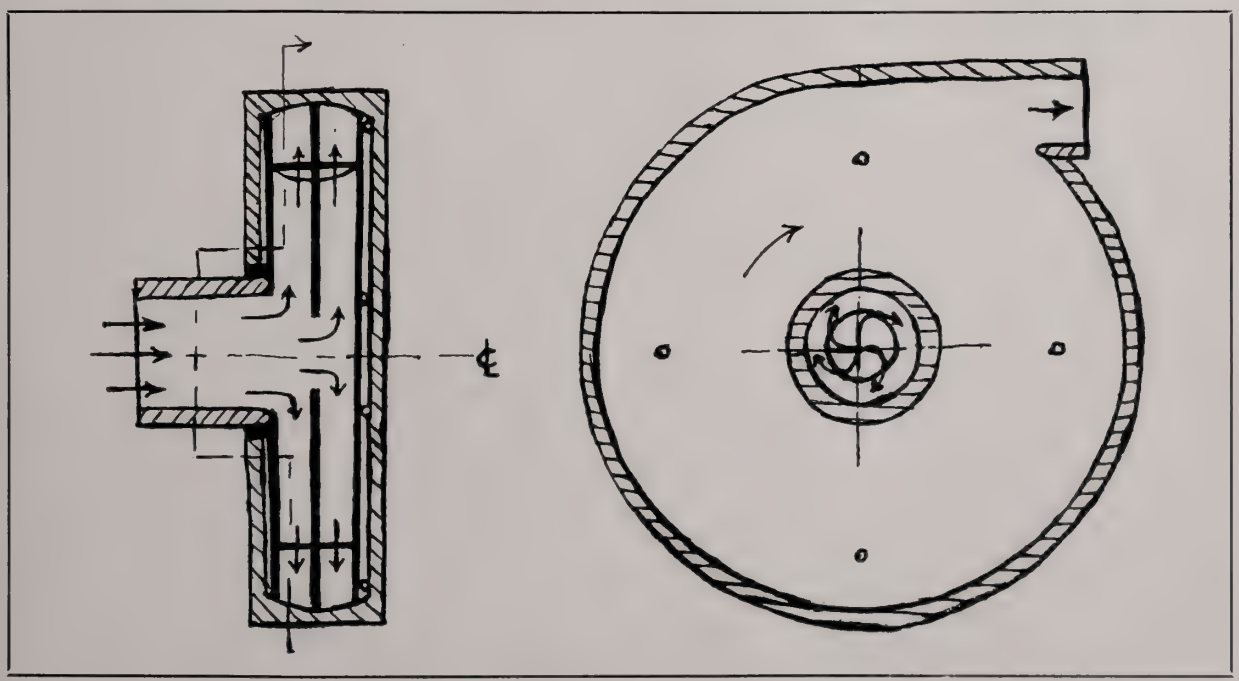


Fig. 5—Schematic cross-sections of optimized design.

a unique pumping principle. It has high efficiency and the ability to handle blood atraumatically. It is proposed that it will find application for both intracorporeal and extracorporeal uses, and for use in other situations when gentle handling of a fluid medium is desired. Based on our preliminary *in-vitro* findings it is our opinion that the perfection of this type of pump could represent a breakthrough in the search for a pump to ultimately serve as an artificial heart. Further studies are under way to optimize the unit.

Acknowledgments

We are deeply grateful to Dr. Fred B. Vogt, Chairman, Department of Biomedical Engineering, Graduate School of Biomedical Sciences at Houston, and Louis Meharg, Ph.D. (E.E.) of the Department of Biomedical Engineering, Graduate School of Biomedical Sciences at Houston for their review and analysis of our results and calculations.

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Ortner's Syndrome

Laryngeal paralysis due to compression of the recurrent laryngeal nerve has been reported to occur in certain types of heart disease. Alexander first described these related conditions in 1904. The syndrome has been reported in one patient with mitral disease and in another patient who showed cardiosclerosis with hypertension and heart failure. When the laryngeal paralysis occurs on the left side, it is a result of recurrent nerve compression caused by dilatation of the left branch of the pulmonary artery just below the arch of the aorta.

Durham, Robert H.—Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

What Is Wrong?

When you talk with the patient, you should listen first for what he wants to tell, secondly, for what he does not want to tell, thirdly, for what he cannot tell. He does not want to tell things the telling of which is shameful or painful. He cannot tell you his implicit assumptions that are unknown to him, such as the assumption that all action not perfectly good is bad, such as the assumption that everything that is not perfectly successful is failure, such as the assumption that everything that is not perfectly safe is dangerous.*

*Henderson, L. J., in Richard Magraw: Ferment in Medicine, 1966.

He that takes medicine and neglects diet, wastes the skill of the physician.—Chinese Proverb

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Two cheers for democracy: one because it admits variety and two because it permits criticism.—E. M. Forster

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We do not free ourselves from something by avoiding it, but only by living through it.—Cesare Pavese

Cesarean Hysterectomy*

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BECAUSE OF A recent trend in some centers toward performing hysterectomy after indicated cesarean section when future pregnancy was contraindicated, we reviewed the experience with cesarean hysterectomy at the Mayo Clinic in the past 15 years.

History of Cesarean Hysterectomy

Early in the 16th century the first cesarean section was performed. The operation at that time was used primarily to save the life of the infant. The mother often died of exsanguination or peritonitis, since the uterine wound was usually left open. The first cesarean hysterectomy, a subtotal procedure to control bleeding, was reported by Bixby[1] in 1869; unfortunately, the woman died 78 hours after the procedure. In 1874, Porro first showed experimentally in rabbits that the death rate was reduced after cesarean section by removal of the uterus. This principle was applied by Porro[2] in 1876, when he performed the first successful cesarean hysterectomy. Harris[3] reported that from 1876 to 1880 there were 50 cases of cesarean hysterectomy, with a maternal mortality rate of 58%. Opposition to the removal of the uterus was voiced in 1882 by Sänger,[4] who indicated that closure of the uterine wound with sutures eliminated the necessity for removal of the uterus. Early in the 20th century, intrapartum infection became the most important indication for cesarean hysterectomy. In 1952, however, Kobak and associates[5] reported that none of the 200 women severely infected after cesarean section who were treated with antibiotics died; thus, infection as an indication for cesarean hysterectomy was seemingly eliminated.

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*Read at the meeting of the Minnesota Obstetrical and Gynecological Society, Minneapolis, December 2 to 4, 1966.

See editorial page 49.

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‡Mayo Clinic and Mayo Foundation: Section of Gynecologic Surgery.

Prior to 1950, cesarean hysterectomy was usually carried out as emergency treatment for overwhelming infection or for control of hemorrhage. Of late, the operation has been done electively in some centers for a variety of indications, most commonly in women near the end of their reproductive period in whom the uterus no longer serves a useful function. Davis,[6] after a review in 1951 of 140 cases of total cesarean hysterectomy, and Montague,[7] after a study in 1959 of 75 such cases, stated that cesarean hysterectomy is the procedure of choice when both cesarean section and sterilization are required. Pletsch and Sandberg,[8] in 1963, also supported this thesis. They stated the belief that a relatively minor operation cannot be entirely justified if a more extensive procedure offers greater advantages to the patient without unduly increasing the risk. A rather different viewpoint was expressed by O'Leary and Steer[9] in 1964. They concluded that cesarean hysterectomy was associated with greater blood loss at surgery, an increased incidence of urinary tract injury, and a higher rate of morbidity. This statement was based on the review of 165 cases of cesarean hysterectomy. Two thirds of the patients required blood transfusions during or after the procedure. There were four bladder perforations and two vesicovaginal fistulas. The morbidity rate was approximately twice as great when compared to the morbidity rate associated with cesarean section followed by tubal ligation. They also noted that it was difficult to determine whether the cervix was totally removed at cesarean hysterectomy. This difficulty partially defeated the purpose of the procedure in prevention of future gynecologic disorders. In 1957 Dyer[10] reported cerebral thrombosis, peritonitis, and pulmonary embolus in his extensive series involving cesarean hysterectomy.

Present Study

The records of patients who had had cesarean section performed at the Mayo Clinic from January 1952 to September 1966 were reviewed. During this period there were 23,189 deliveries, of which 789 were by cesarean section. Tubal ligation was done at cesarean section on 64 occasions, and there were 25 cesarean hysterectomies.

*See Test Your Word Score Page 53.

The 25 cesarean hysterectomies may be subdivided into two major groups: emergency cesarean hysterectomy as a life-saving procedure to prevent exsanguination during cesarean section, and elective cesarean hysterectomy when the operator judged that the future health and well-being of the patient would be best served by removal of the uterus at cesarean section. Elective cesarean section was always performed for obstetric indication and hysterectomy for a separate indication. There were 23 total cesarean hysterectomies, and two subtotal procedures. One subtotal hysterectomy was performed because of hemorrhage and shock and the other because of sepsis. Emergency cesarean hysterectomy was carried out in seven instances: four for abruptio placenta, two for acute rupture of the uterus, and one for placenta percreta.*

Indications

Malignancy

Eighteen of the cesarean hysterectomies were classified as elective: five involved cancer and 13 involved benign conditions. In two cases the Wertheim-type hysterectomy was carried out at cesarean section for stage I carcinoma of the cervix. In two cases—one of carcinoma of the ovary associated with pregnancy and the other of carcinoma of the bowel associated with pregnancy—radical procedures were done. The fifth case was one of cancer of the breast, with metastatically involved axillary lymph nodes in which oophorectomy was indicated. The uterus was also removed at that time. In the 13 cases in which the uterus was removed because of various benign conditions, the most frequent indication was the presence of multiple uterine leiomyomata; these were noted in five cases. The next most frequent indication was that of a defective uterine scar, occurring in four instances. Two uteri were removed because of prolonged labor with incipient intra-uterine infection. Two others were removed because of extensive uterine damage not associated with hemorrhage. There was one case in which the mother had undergone multiple procedures for an imperforate anus; an anomalous uterus was removed at cesarean section. In no case was cesarean section carried out solely for the purpose of steri-

lization.

Morbidity and Complications

As might be expected in the group who underwent emergency cesarean hysterectomy, the incidences of blood loss and morbidity were high (morbidity being defined as a temperature of 100.4 F on any two postoperative days). In one patient with placenta percreta, 31 units of blood were infused. This patient had had a temperature of more than 100.4 F. on 11 postoperative days. Cardiac arrest occurred, requiring defibrillation, and a tracheotomy was necessary to relieve obstruction. The patient is alive and well. One woman with abruptio placenta required eight units of whole blood during removal of the uterus and had fever for three days. Another woman, with traumatic extension of the uterine incision, also required eight units of blood and had fever for four days.

The morbidity associated with elective cesarean hysterectomy for cancer was surprisingly low. One patient with stage I cancer of the cervix required two units of whole blood during surgery and had a temperature of more than 100.4 F. for three days. In the group undergoing elective surgery because of benign conditions, one patient required three units of whole blood during removal of the uterus for multiple uterine fibroids, and another required two units of whole blood during hysterectomy for prolonged labor and probable uterine infection. The first patient had a fever for two days, and the second for four days. In the group undergoing elective cesarean hysterectomy, there was one maternal death, a 42-year-old woman, gravida 1, who underwent cesarean section because of pelvic contraction and nulliparity. This patient had suffered for years from a congenital prolapse of the uterus in which the cervix and lower uterine segment protruded 4 cm. beyond the vulva. During the course of the hysterectomy the bladder was opened. Intravenous tetracycline was administered during the postoperative course. Azotemia and jaundice developed, and the patient died on the twelfth postoperative day. Autopsy revealed acute, yellow atrophy (fatty infiltration) of the liver, with bile necrosis.

Thus for both the emergency and the elective group, the rate of morbidity was 24%, and for the elective group alone it was 15.4%. All patients who had morbidity also had significant blood loss.

Fetal Outcome

In the group undergoing emergency cesarean section, there were five full-term infants, three of which were stillborn and two of which survived; there were two premature infants, both of them stillborn. In the five cases involving treatment of carcinoma, two infants weighing more than 2,500 cm. survived, and three infants weighing less than 2,500 cm. were stillborn. All infants in the 13 remaining cases of elective cesarean section survived.

Discussion

If the results of cesarean section followed by hysterectomy are to be compared with those of cesarean section followed by tubal ligation, only conditions that allow a choice of either procedure should be studied. Eliminated, therefore, from the comparison should be all cases of emergency cesarean hysterectomy carried out as a life-saving measure in which no choice but removal of the uterus was available. Also eliminated from comparison should be cases in which extensive surgical procedures for treatment of carcinoma are involved. We are left with a group of truly elective conditions, in which the surgeon is faced with a choice of removing the uterus or ligating the tubes. Specifically, in this series are the cases that involved uterine myomas, defective uterine scar, probable uterine infection, uterine prolapse, and multiple congenital anomalies.

In 1965, Jensen and Aaro[11] reviewed all cases involving cesarean sections at the Mayo Clinic during the previous 10 years and reported that there were 532 cesarean sections carried out—an incidence of 3.3% of all deliveries. Morbidity, as defined by the joint committee of maternal welfare, was noted in 10.3% of the cases. The most common causes were endometritis, urinary-tract infection, and pneumonitis. There were three cases of wound infection, one case of deep thrombophlebitis, and one of pelvic hematoma. The average number of febrile days in their series was 2.8.

Thirty-five patients in Jensen and Aaro's series had tubal ligation; none required blood transfusion and six experienced morbidity (17.1%). There were no complications or deaths in the group that underwent cesarean section and tubal ligation.

Also to be considered is the patient with uterine disease necessitating hysterectomy. Some authors have stated that cesarean hysterectomy is indicated in these cases. When defined in terms of temperature, morbidity in cesarean hysterectomy is comparable to that in hysterectomy alone. However, the serious complications of urinary-tract injury and excessive blood loss associated with cesarean hysterectomy eliminate this operation as an elective procedure.

Conclusion

Throughout the literature and in the present series, cesarean hysterectomy has been shown to be a life-saving measure in conditions causing acute blood loss during indicated cesarean section. But elective cesarean hysterectomy, both in this series and in others, is associated with an unacceptably high primary morbidity and complication rate. However, balanced against this increased morbidity and complication rate is the long-term consequence of leaving an abnormal uterus in situ. Large fibroids may degenerate, or they may be associated with subinvolution of the uterus and delayed hemorrhage. Low-grade endometritis, especially in an extensively damaged and repaired uterus, may become an overwhelming peritonitis. Ligated uterine tubes occasionally regain patency. The surgeon, then, must weigh the acceptable morbidity in cesarean hysterectomy against the seriousness of the disease present. When indicated cesarean section is associated with relatively minor uterine disease, the conservative course favors cesarean section and tubal ligation. Cesarean hysterectomy should never be carried out when sterilization is the only indication.

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Zonotherapy

One Dr. Fitzgerald of Hartford, Connecticut, has divided the body into zones, lengthwise and crosswise, and heals disease in one zone by pressing on others. To keep the pressure going he developed little wire springs. For instance, a toothache on the right side may be "cured" by fastening a little spring around the second toe of the left foot. Naturally, Fitzgerald has never convinced anyone with ordinary reasoning powers that there is anything in his system—except what he gets out of it.*

*Morris Fishbein, M.D.: New Medical Follies, 1927.

Opportunity

Opportunity seldom calls on people who aren't worth a rap and who can't stand a knock.—David T. Armstrong

Nafcillin for Prophylaxis in Oral Surgery

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Members of our group have previously reported data on the use of phenoxymethyl penicillin, erythromycin, and cloxacillin for the prevention of postoperative bacterial invasion of blood after oral surgical procedures.[1-5] In continuing these studies, nafcillin (Unipen), a semisynthetic penicillin containing an ethoxynaphthyl side chain, was used. On oral administration, nafcillin produces serum levels that may be lower than those obtained with oxacillin, but nafcillin persists longer in the serum and may provide better tissue penetration.[6] The purpose of this study, as it has been with the others, was to test the effectiveness of the selected antibiotic agent under the conditions outlined.

Methods and Materials

The patients were selected for this study solely on the basis of their need of oral surgical procedures. The surgical problems consisted mostly of impacted third molars and full-mouth extractions because of periodontal disease or caries or both. Nafcillin† in capsule form was administered orally to 29 patients in four successive doses of 250 mg., beginning 18 hours prior to operation. An additional 25 patients received 500 mg. of nafcillin orally in four successive doses, also beginning 18 hours prior to operation. Blood for cultures was drawn immediately after the operative procedure, while the patient was still in the operating room, and again approximately 18 hours later. No patient was included who had either preexisting or known infection, valvular heart disease, or a combination of these problems. Of the initial group of 29 patients, 10 had positive cultures of the blood obtained immediately after the surgical procedure (Table). In all 10, cultures of the blood obtained 18 hours after operation were negative. Of the 25 patients to whom 500 mg. of nafcil-

*Mayo Clinic and Mayo Foundation: Section of Dentistry.
**Mayo Clinic and Mayo Foundation: Section of Medicine.
†Supplied as Unipen, courtesy of Wyeth Laboratories, Philadelphia.

lin had been administered, three had positive cultures of the blood obtained immediately after the surgical procedure. However, all three cultures obtained 18 hours after operation were negative.

Comment

It is noteworthy that blood cultures in eight of the 10 patients receiving the 250-mg. dosage of nafcillin yielded *Streptococcus mitis*. The remaining two cultures were positive for *Bacteroides* and an anaerobic streptococcus. Of the three patients having positive cultures after oral administration of the 500-mg. dosage of nafcillin, all cultures yielded *S. mitis*. Despite the improved results after the higher dose of nafcillin, they did not approximate those noted in our patients who received optimal amounts of phenoxymethyl penicillin[1-3] or erythromycin[5] before operation and in whom cultures for *S. mitis* were consistently negative. As was true in our study of cloxacillin, these findings were not anticipated prior to our investigation, since nafcillin is generally considered effective against *S. mitis*. We had concluded a priori that the effect of nafcillin would likely be similar to that of phenoxymethyl penicillin and erythromycin against most organisms inhabiting the oral cavity, and that its antistaphylococcal effect would be greater than that of phenoxymethyl penicillin. The latter effect appears to have been achieved, since blood cultures from patients in the present series failed to grow staphylococci, in contrast to that seen in six of 94 patients receiving phenoxymethyl penicillin.[1-3] Nafcillin's antistaphylococcal effect under the conditions outlined is similar to that of erythromycin[4] and exceeds that of cloxacillin.[5] No patient who received nafcillin in either dosage form had positive cultures of blood taken 18 hours after operation. This finding can be contrasted to that encountered in our study employing cloxacillin, wherein two of 52 patients had positive cultures 18 hours after surgery.[5]

Data from the present study indicate that patients undergoing dental surgery should receive individual doses of 500 mg. of nafcillin rather than 250 mg. In this regard, there is general agreement that serum levels of nafcillin are higher when the subject is fasting and has had repeated doses. If decreased intestinal absorption of nafcillin were due to food ingested in the 18 hours before surgery, perhaps the increased dosage would result in higher serum levels and a more desirable antibacterial effect. Perhaps a more desirable antistreptococcal effect would result from the administration of nafcillin at intervals of every four hours for 24 hours, or even 48 hours, preoperatively. In any event, we recommend nafcillin in the dosage of 500 mg. in attempts to prevent bacterial invasion of the blood after oral surgical procedures.

Summary

Twenty-nine patients received nafcillin in amounts of 250 mg. in four doses by the oral route beginning 18 hours before oral surgery. In 10 of the 29 patients, cultures of blood drawn immediately after the operation grew bacteria. Eight of the 10 positive cultures grew *S. mitis*, one culture grew *Bacteroides*, and another grew an anaerobic streptococcus. Cultures of blood drawn 18 hours after operation in all 29 patients failed to grow any bacteria.

Twenty-five patients received nafcillin in amounts of 500 mg. in four doses by the oral route beginning 18 hours before oral surgery. Three of these patients had positive cultures of blood drawn immediately after operation.

TABLE
Positive Blood Cultures After Oral Operations With Nafcillin Administered Preoperatively in 54 Patients

Group	Dose*	Microorganism	Time after operation	
			Immediately	18 hours
29 patients	250 mg.	*S. mitis*	8	0
		Bacteroides	1	0
		Anaerobic streptococcus	1	0
25 patients	500 mg.	*S. mitis*	3	0

*Every four hours for four doses beginning 18 hours before operation.

All three were positive for *S. mitis*. Cultures of blood drawn 18 hours after operation in these 25 patients failed to grow any bacteria.

These findings can be contrasted to our experiences with patients who have received optimal amounts of phenoxymethyl penicillin or erythromycin preoperatively and in whom cultures for *S. mitis* have been consistently negative. Under the conditions of our studies, nafcillin's antistaphylococcal effect was similar to that of erythromycin and exceeded that of cloxacillin. In this same regard, nafcillin was more effective than cloxacillin in assuring negativity of cultures of blood obtained 18 hours after operation.

Acknowledgment

The authors wish to express appreciation to G. M. Needham, Ph.D., of the Section of Microbiology for his assistance in this study.

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Papyrus Ebers
For Pains in the Limbs

'For Pains in All the Limbs' the Scribe (of the Egyptian Papyrus) made a good start by instructing the Patient to mix up Castor Oil with Honey; but in the next few lines he spoilt everything by telling him to smear this all over the outside of his body instead of swallowing it and allowing it to do its work internally. Of course having got off the track at the start he found it impossible to right himself and accordingly went from bad to worse, his next effort being a poultice of Locusts which have been ground up in a mortar with Butter and Spices. For 'Pains in the Bones in Every Limb according to the Truth,' he recommended a poultice of Black Knife-stone with Fat, Honey, and Saltpetre as adjuvants. But according to the truth as we know it the use of Black Knife-stone, with or without Fat, Honey, and Saltpetre, in this connection is entirely fallacious, and not to be commended. The same can be said of the special poultice for the Thigh:

Bean-meal
Meal-of-the-pesen-bread
Sea-salt
Human Urine
Cook into one and apply as a Poultice.

And also for the Front-of-the-Shins, which was, however, let down more lightly:

The Inner-of-the-Shadfish; what is found in its Head.
Soak in Honey and apply as a Poultice.
It will heal the patient forthwith.*

*Bryan, Cyril: The Papyrus Ebers, D. Appleton and Company, New York, p. 60-61, 1931.

The Clyster

The clyster or enema was practiced by the Egyptians in all its intimate refinements. They were reputed to have learnt it from the sacred ibis. When constipated this intelligent bird relieved itself with its curved beak aided by its very long neck. The Egyptians were quick to learn and imitated the ibis, using an instrument in the shape of the bird's beak. In the fifteenth century the clyster syringe was rediscovered by Professor Gatenaria of Pavia.

This syringe was hailed with undisguised joy, particularly in France. For three hundred years the enema was one of the favourite remedies in all cases of physical discomfort. During the first years of the reign of Louis XIV, it was the mode at the French court. Ladies and dandies alike had three to four enemas a day in order to acquire a fresh and healthy complexion and the rich bourgeoisie did not lag behind.

There was a great choice of cylster mixtures, including extracts of orange blossom, angelica, bergamot and roses. The ladies of the Faubourg St. Germain, that classical home of boudoir erotics, concocted their own clysters from secret recipes whose ingredients they would not betray even to their best friends.

In those gallant days of the Rococo Age, when the syringe stood at its peak of fame, artists vied with each other to combine esthetic shapes with elegance and convenience in handling. Instruments, real works of art in their way, were made from tortoiseshell or mother-of-pearl inlaid with silver gilt. The expensive decoration delighted the eye and made people forget the unappetising purpose of the instrument.

To administer an enema "professionally" was considered a high art. The operator must not take the place by storm but like a trained sharp-shooter prepare for action and fire as soon as he catches sight of the enemy. The operator must also behave with dexterity and consideration and refrain from any movement until he has the target in sight. Then he must kneel down with deference, bring up the instrument with the left hand without undue haste or eagerness, lower the pressure pump *amoroso,* and set it in motion *pianissimo,* with care and without jerking.

The clyster became the ally of blood-letting and purging—an unholy trinity which the doctors let loose on the human race. Persons of quality and crowned heads in particular who were in the hands of the leading physicians felt the healing lash of this three-thonged knout. Within six months Louis XIII of France was subjected to 47 bleedings, 215 purgings and 312 clysters —two every day except holidays. His son, Louis XIV, would presumably have suffered worse had he not rebelled against the prescriptions of his doctors. During his reign he got away with a mere 38 blood-lettings. Nor were enemas particularly to his taste, and the doctors only managed to force a few hundred on him. On the other hand, he endured several thousand purgings, which his gluttony necessitated, in order to unburden the royal bowels. The record of cathartic therapy was undoubtedly held by King Charles II of England, who had to endure untold agonies before he was allowed to die, presumably of a brain hemorrhage.*

*H. S. Glasscheib, M.D.: The March of Medicine, 1964.

Optimism

An optimist is a fellow who takes the cold water thrown on his ideas, heats it with enthusiasm, makes steam, and pushes ahead.—Megaphone

Smears from the Cervix

Cancer Cell Detection

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THIS REPORT is limited to a study of the results of examinations of smears from the cervix uteri submitted to us for cancer cell detection over a ten-year period by 99 physicians in 28 regional cities. There were 62,185 patient examinations. An unknown number of these smears were repeat examinations on the same patients during this period. Our five pathologists found 1,042 of these examinations showed positive smears (Table 1). Among these cases there were 395 women with proven malignancies of the uterus. These patients were treated for their carcinomas of the uterus in many of the communities from which the smears were sent.

During the first year (1956) of this ten-year period there were 1,764 women whose smears were examined (Figure 1). In 1965 there were 11,377 patients' smears studied. Thus during the ten years there was an average increase of 1000 examinations a year for a total of 62,185. The percentage increase in number of examinations compared to the total tests performed per year gradually fell from 57% to 8%.

Diagnoses

Table 1 has the distribution of numbers of patients found to have positive smears in the Papanicolaou classes II to V using our modified definitions of the classes (Table 1). Since there were 395 women with malignancies, and only 26% or 105 of these malignancies were considered clearly cancer cells or class V, one must conclude that this probably reflects some uncertainty and lack of experience, especially in the early years of our study period.

Carcinoma in Situ

The informative Table 2 reveals that in those patients with *original* class II smears in which tissue diagnoses were made, there was a

*Pathology Service of St. Luke's Hospital, Duluth, Minnesota.

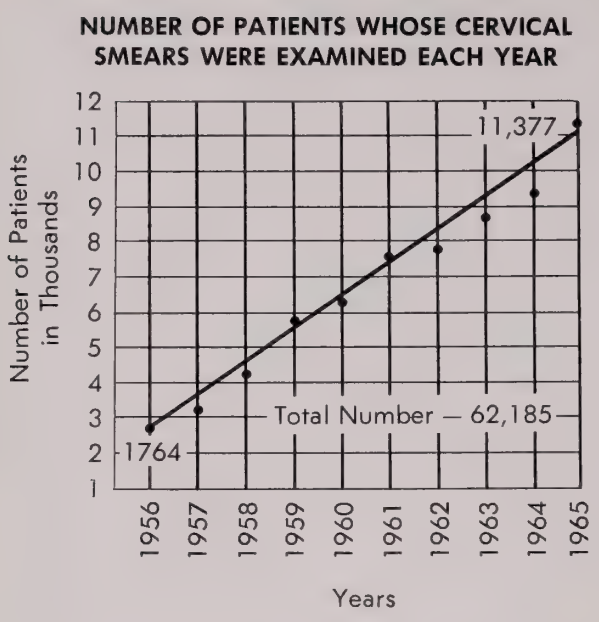


Figure 1

33% chance of the cervix having a carcinoma in situ. One should take into account that these patients had subsequent smears with higher class readings; otherwise a biopsy or more extensive surgical procedure probably would not have been done. As seen in Table 1, there were 355 class II readings, only 27 of which had tissue diagnoses. Ashe and Arey[1] found that 6.4% of their patients with cervical malignancies had class II readings on their original cervical smears.

Ninety-four per cent of the patients with carcinoma in situ of the cervix had original cervical smear readings in classes III, IV or V. With increasingly higher class readings the certainty of malignancy increased to class V where 91% of the patients had a uterine malignancy. During the ten-year period it was brought to our attention that we had made false-negative smear readings on two patients. These patients with carcinoma in situ of the cervix were found to have positive smears in the previous two weeks. The second cervical smear might very well be negative when a small area of malignancy has been rubbed off the cervix by the first examination. Time should be permitted for the cervix to recover from the trauma of the smear test before another smear or tissue diagnostic procedure is performed. The malignant lesion is sometimes lost as a result of surgical procedures. Thus a benign reading of tissue following conization may be a false-negative diagnosis and should have follow-up smears.

There were 334 patients with proven squamous cell carcinoma in situ of the cervix: 0.53% of the 62,185 examinations. This compares with 0.36% of 108,000 women found to have the same malignancy in a "Population Screening" project[2] in Memphis.

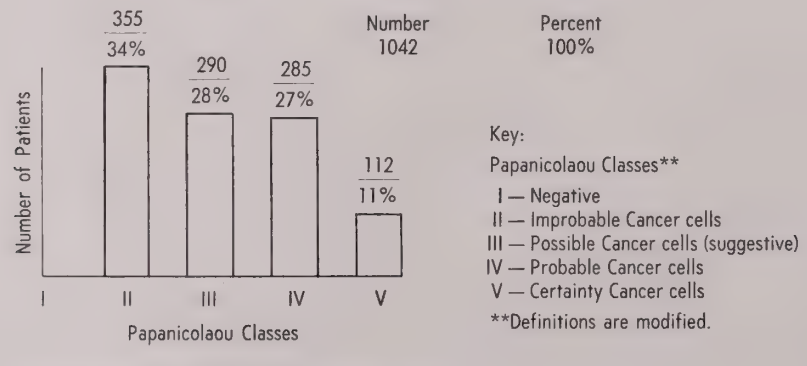
Invasive Carcinoma

It is apparent from Table 3 that conization of the cervix is valuable but not infallible in the diagnosis of carcinoma in situ. Eight or three per cent of the patients whose cone revealed an in-situ malignancy later were found to have an invasive squamous cell carcinoma in the hysterectomy specimen.

Ages of Patients

In Table 4 one finds the age groupings of

TABLE I
FREQUENCY OF POSITIVE DIAGNOSES IN FOUR CLASSES*



*One smear per patient. The highest reading counted.

328 patients with carcinoma in situ of the cervix. The average age is 45.8 years—considerably younger than the average of 53 years in 51 women with invasive squamous cell carcinoma of the cervix (Table 5). Many authors[3,4,5] agree that one might expect to find either malignancy at almost any age. There is a ten-year variation in the average ages of women with either of these malignancies. Our averages are the highest found. In each group study, the eight to ten-year difference between the average of women with in-situ and invasive malignancies is constant and probably an indication of the time required for the in-situ carcinoma to become invasive.

Signs and Symptoms

An attempt to get reliable statistics on the appearance of the cervix with squamous cell

TABLE 2
Correlation of Original Cytology with Final Tissue Diagnoses—533 Patients

Pathology	Class II		Class III		Class IV		Class V	
	No.	%	No.	%	No.	%	No.	%
Benign	12	44	31	18	22	10	5	4
Dysplasia (atypia)	1	4	28	17	19	9	1	1
Carcinoma in Situ	9	33	86	51	162	73	77	67
Carcinoma—Invasive	0	0	13	8	18	8	28	24
Unsatisfactory Cone	0	0	1	1	0	0	0	0
Adenoca. of Cervix	3	11	2	1	0	0	1	1
Adenoca. of Endom.	0	0	7	4	2	1	1	1
Others	2	7	0	0	0	0	2	2
TOTALS	27	100	168	100	223	100	115	100

TABLE 3
Residual Tumor in Hysterectomy
Previous Cone with Carcinoma in Situ

Tissue Diagnosis	No. Pts.	Percent
Carcinoma in Situ	138	55
Invasive Carcinoma	8	3
Dyplasia	4	2
No Residual Cancer	103	40
TOTALS	253	100

TABLE 4

AGES OF PATIENTS WITH CARCINOMA IN SITU OF CERVIX

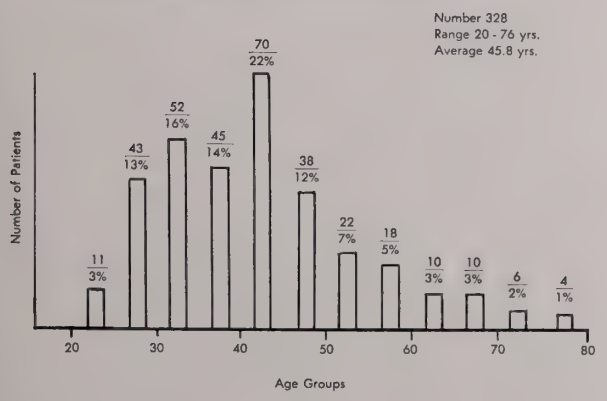
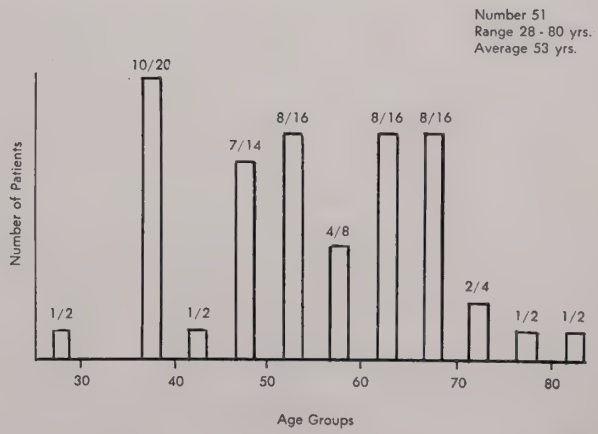


TABLE 5

AGES OF PATIENTS WITH INVASIVE SQUAMOUS CELL CARCINOMA OF CERVIX



carcinoma in situ was not possible with our sources of information. The frequency of symptoms and signs of cervices with this malignancy varies considerably in different groups reported.[3,4,5,8,9] Among others, Guseberg and Marshal[9] conclude that there are no characteristic signs or symptoms. Our physicians apparently did their surgical diagnostic procedures on the basis of the positive cervical smears and generally made little mention of the appearance of the cervix. Discussions with many of the physicians plus the great dominance of normal cervices when they were described in the charts lead to the speculation that in the majority of patients the cervices were entirely normal and the remainder probably had no more changes than might be expected in the average run of women.

It became apparent in this study that smears were frequently not taken from cervices with obvious carcinomas of the cervix. The great majority of these patients were diagnosed by small biopsies and immediately treated by radiation therapy. This accounts for the relatively few patients (51) with invasive carcinomas of the cervix in this study.

*See Test Your Word Score Page 53.

TABLE 6

First Therapy for Cure in Cases of Squamous Cell Carcinoma In Situ of Cervix

Therapy	Number Patients	Recurred	Apparent Cures
Abdominal Hysterectomy	178	5*	173
Vaginal Hysterectomy	48	0	48
Conization of Cervix	62	5*	57
Trachelectomy	2		2
Irradiation	1		1
Cauterization	0		
Other			

*Vaginal recurrences eventually cured.

TABLE 7

Therapy for Invasive Squamous Cell Carcinoma of Cervix

Therapy	Number Patients	Recurred	Apparent Cures
Irradiation Alone	36	6	30
Irradiation & Hyst.	4	0	4
Hysterectomy Alone*	11	1	10

*Stage I Carcinoma

TABLE 8

Infectious Agents—53,607 Patients

Agents	Number Patients	Percent	Recent Experience
Trichomonas Vaginalis	2,083	3.9%	6%
Monilia	871	1.6%	2%

Treatment

Of the 226 attempts at cure of squamous cell carcinoma in situ of the cervix by hysterectomy there were five superficial recurrences on the adjacent vaginal surface (Table 6). These were discovered by follow-up smears and apparently cured by radiation therapy. There was a remarkable success of treatment of the 62 patients with in-situ carcinoma by conization and follow-up smear technique. Only 5% of this group had recurrence and were apparently cured by later hysterectomy. It will be noted in Table 3 that only 103 or 40% of the patients were apparently cured by the conization prior to hysterectomy. Our only explanation for this paradox is that some surgeons do a more extensive conization than others. This may be especially true if they wish to attempt a cure and not simply obtain tissue for a diagnosis. Giglio, Dowling and Jones[10] have concluded that conization alone is inadequate treatment, since in their experience 19% of the uteri had residual carcinoma after the conization.

A relatively high cure rate occurred in the invasive squamous cell carcinoma of the cervix group, where 30 of 36 patients were apparently cured by radiation therapy (Table 7). Hysterectomy alone in eleven women with superficial invasion (Stage 1) was followed by 10 apparent cures.

Non-Neoplastic Diagnoses

Trichomonas vaginalis* and Monilia require special attention and training to find them in cervical smears. Our early results had a much lower yield of positive organisms than later experience. Even today rushed examinations miss the diagnosis. Recently we have found 6 per cent of the patients to have trichomoniasis and 2 per cent moniliasis (Table 8).

A brief scan of a smear from the cervix in trained hands can permit an estimation of the maturation index of acceptable accuracy. It is generally agreed that a smear prepared from the surface cells of the vaginal wall in the

cul-de-sac area is more suited for cytohormone analysis. In spite of alterations by infections of the cervix and by scraping techniques of the cervical smear taken for cancer cell detection the rapid estimation of percentages of superficial cells, intermediate cells and parabasal cells yields sufficient information concerning the hormone status of most patients to warrant their usage routinely with cancer cell detection methods.

Costs

Handy and Wieben[11] report that their routine cervical smear examination of all hospital admissions in 25 participating hospitals during 1963 cost the New York State Health Department $718 (seven hundred and eighteen dollars) per confirmed case of malignancy found. Our ten-year experience with 62,185 women cost the patients examined $787 (seven hundred and eighty-seven dollars) per malignancy found. As indicated above, the great majority of our group of women with an obvious lesion of invasive carcinoma of the cervix did not receive a smear examination but did have the more efficient and direct biopsy. Thus the cost per case of malignancy found was increased in the remaining women examined. Considering the added sophisticated information on cytohormone analysis and trichomonas infestation given by our private enterprise, the added expense, if any, does appear to compare favorably with a large scale public health program.

Conclusions

1. A ten-year total of 62,185 patients had cervical smear examinations leading to the final diagnosis of uterine malignancies in 395 patients, an incidence of 0.63% in the examinations which included numerous repeat smears on the same patients.
2. Of the 62,185 examinations 1042 or 1.6% showed positive smear readings, 38% of these uterine malignancies.
3. Cervical smear examinations have increased by 1000 patients per year for the last ten years.
4. Although the average age of 328 women with squamous cell carcinoma in situ of the cervix was 45.8 years and that of the 51 women with the invasive variety was 53 years, both types of lesions occur at practically all ages.
5. Original class II readings on cervical smears should be followed by negative readings before being dismissed as unimportant.
6. With increasingly higher class readings on cervical smears the certainty of malignancy increased to class V where 91% of the patients had a malignancy.
7. The typical cervix with carcinoma in situ is a normal-appearing cervix.
8. All 226 patients treated by hysterectomy for carcinoma in situ of the cervix were apparently cured after five vaginal surface recurrences were detected by follow-up smears and treated.
9. There is a local trend to treat carcinoma in situ of selected patients by cervical conization and follow-up smears. Thus in 62 patients there were five recurrences which were then apparently cured by hysterectomy.
10. The question is raised whether bilateral oophorectomy at the time of hysterectomy for carcinoma in situ of the cervix does more harm than good?
11. Trichomonas vaginalis occurs in approximately 6% and moniliasis in 2% of the patients examined.
12. Routine maturation index estimations on cervical smears are frequently useful for selected patients.

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4-11. May be secured from the author or the reprints.

A lady is a woman who makes a man behave like a gentleman.—Russell Lynes

Medicine and Religion

I have been to dinner with a group of doctors—they were talking freely among themselves, and they were sufficiently self-confident not to be afraid of saying unconventional things—when they began to discuss the possibility of a radical attack upon the degenerative disease known as old age. They did not consider it beyond all possibility of medical attack, but rather looked forward to the day—perhaps not too far in the future—when the time of inevitable death should be rolled back, perhaps into the indefinite future, and death would be accidental, as it seems to be with giant sequoias and perhaps some fish.

I am not saying that they were right in this conjecture (and I am quite sure that they would not claim it to be more than a conjecture), but the weight of the names supporting it was too great to allow me to reject the suggestion out of hand. Consoling as the suggestion may seem at first sight, it is in reality very terrifying, and above all for the doctors. For if one thing is clear, it is that humanity as such could not long survive the indefinite prolongation of all lives which come into being. Not only would the nonself-supporting part of humanity come to outweigh the part on which its continued existence depends, but we should be under such a perpetual debt to the men of the past that we should be totally unprepared to face the new problems of the future.

It is unthinkable that all lives should be prolonged in an indiscriminate way. If, however, there exists the possibility of indefinite prolongation, the termination of a life or even the refusal or neglect to prolong it involves a moral decision of the doctors. What will become of the traditional prestige of the medical profession as priests of the battle against death and as ministers of mercy? I will grant that there are cases even at present when doctors qualify this mission of theirs and decide not to prolong a useless and miserable life.

But what if such decisions, instead of being rare and unmentioned, will have to be made, not in a few special cases, but in the case of almost every death? What if every patient comes to regard every doctor, not only as his savior but his ultimate executioner? Can the doctor survive this power of good and evil that will be thrust upon him? Can mankind itself survive this new order of things?*

*Norbert Wiener: God and Golem, Inc., M.I.T. Press, 1964.

DERIVATIVELY SPEAKING

Scrofula—from Latin *scrofa* (brood sow), perhaps from a fanciful resemblance of the glandular swellings to little pigs.

The Journal of the American Medical Association reports this incident at the Mayo Clinic: A lady psychiatrist was questioning a patient and asked: "What would you say would be the difference between a little boy and a dwarf?" . . . The patient thought a while and said: "Well, there might be a lot of difference."

"What for instance?" asked the psychiatrist encouragingly.

"Well", replied the patient, "the dwarf might be a girl."

The Difference

"Hurrah!" cried the optimist, "I am finally at the end of my difficulties!" "Yes," murmured the pessimist, "but at which end?"

Dermoid Cyst Coincident with Stein-Leventhal Syndrome

Report of Case

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CONCOMITANT OVARIAN neoplasms in Stein-Leventhal syndrome are rare. Only isolated cases have been reported. Papillary cystadenoma,[1] thecoma,[2] arrhenoblastoma,[3,4] Leydig cell tumor,[5] adenofibroma,[6] and papilloma[6] have been present in ovaries affected by Stein-Leventhal syndrome.

In an analysis of 241 cases of Stein-Leventhal syndrome, Hutchison and associates[6] recently reported 11 cases in which various neoplasms of the ovaries were found. It is of interest that in five of the 11 cases the neoplasms were benign cystic teratomas. Recently, while doing a wedge resection we encountered a dermoid cyst in a polycystic ovary and, because of the rarity of this pathologic finding, we consider the case worth reporting.

Report of Case

A 21-year-old nulligravida Caucasoid woman came to the Mayo Clinic with the presenting complaints of primary sterility and oligomenorrhea. She had been married for 2½ years. Her menarche started when she was eight years old, and the next menstrual period came one year later. Menstruation had always occurred irregularly at intervals of two to 13 months. She had been taking Ortho-novum for about three months. During the course of medication her menstrual periods became regular, but after she discontinued taking this drug, her menses were again irregular.

The patient was five feet, five inches tall and weighed 166½ pounds. The pulse was 100 beats per minute and the blood pressure, 114 mm. Hg. systolic and 78 diastolic. She had moderate acne and the distribution of hair was normal. Her breasts were pendulous and her uterus was small. Results of laboratory tests were as follows: hemoglobin 14.3 Gm.; leukocytes 6,700; sedimentation rate 12 mm. in 1 hour; blood sugar 81 mg/100 ml.; VDRL negative. Urinalysis showed a specific gravity of 1.012, pH acid, sugar negative, and protein grade 1. Seventeen-Ketosteroids measured 10.8 mg. and ketogenic steroids 15.5 mg. The cervical pap smear was negative. Roentgenograms of the chest and skull showed no abnormality. On culdoscopic examination both ovaries were found to be twice the normal size. The capsule of each ovary was grayish white, smooth, and glistening. No evidence of ovulation was noted. Both tubes were visualized and appeared normal.

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A clinical impression of Stein-Leventhal syndrome was made and bilateral wedge resection was advised.

At laparotomy, preliminary dilatation and curettage showed proliferative endometrium. The abdomen was opened through a lower midline incision. There was no endometriosis. A 2-cm. fimbrial cyst was removed from the left tube. The ovaries measured 6 by 4 by 2 cm. with smooth capsules and no evidence of formation of corpus luteum; they were wedged longitudinally and enlarged with considerable cortical fibrous thickening, multiple follicular cysts 0.5 cm. in diameter to microscopic size, numerous developing primordial follicles with corpora atretica, and no corpora lutea. A 2-cm. dermoid cyst of the left ovary was found and removed (Figure). The patient's postoperative course was uneventful and she was dismissed after 11 days.



Figure. Longitudinal wedges from both ovaries with deep-seated dermoid in left ovary.

Comment and Summary

In Stein-Leventhal syndrome, ovarian neoplasia may be benign as well as malignant; thus any ovarian enlargement should be explored. Hormonal therapy is being utilized more commonly to treat these patients,[7-9] and unless one is aware of such coincident pathologic findings, moderate ovarian enlargement may be ignored. A culdoscopic examination should be performed, although in the patient whose case is reported this examination did not reveal the dermoid cyst, and even on exploration it was not obvious.

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Appendicitis on the Frontier

Appendicitis was rare enough to disconcert a cowboy doctor suddenly confronted with it. In eastern Oregon, Dr. J. H. Fell and Dr. James Ashfor diagnosed a cattleman's severe abdominal pain as appendicitis, but neither doctor had ever seen an appendectomy. They anxiously questioned one another as to how the operation should be done. U. G. Cozad, bailiff of the court, overheard the doctors. He told them that a prisoner had committed suicide in the jail the night before.

"Maybe he had inflammation of the bowels," he said pointedly, and suggested a post mortem.

The two surgeons carried out the "post mortem," opened the dead man's abdomen, carefully reviewed their surgical technique, and planned their entry into their living patient. Satisfied with their dress rehearsal, they placed the appendicitis victim on a door stretched between two saw horses in a kitchen and successfully removed his appendix.*

* Richard Dunlop, M.D.: Doctors of the American Frontier.

Chronic Obstructive Airway Disease

Comparison of Match Test and Vitalor with Standard Pulmonary Function Tests

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RECOGNITION OF breathlessness is not difficult, but describing the resultant impairment requires readily available and accurate estimates of pulmonary function. Such estimates may be obtained by using certain tests of pulmonary function. Although the tests are adjunctive to an adequate history and physical examination, an accurate diagnosis of the condition as well as management and treatment of the patient with pulmonary disease may depend on them. Roentgenograms of the chest, electrocardiograms and, in selected cases, blood gas determinations, pulmonary scanning, and angiograms may also be necessary in the appraisal of a pulmonary problem. Estimation of adequacy of pulmonary function is essential in the assessment of operative risk. Significant chronic obstructive emphysema was frequently associated with fatal postoperative complications in a series of 199 surgical procedures.[1]

A type of pulmonary-function testing equipment should be familiar to each of us as clinicians—to enable us to recognize the early reversible cases of chronic pulmonary disease and to follow the course of patients under treatment. More widespread use of tests providing accurate measurements will lead to more effective care of patients. Testing of pulmonary function need not require elaborate equipment.[2] Two relatively simple procedures will be described.

Testing Procedures

Match Test

The patient's attempts, by rapid exhalation through the open mouth, to extinguish a paper match at a distance of six inches (Figure 1) provide an estimate of the severity of pulmonary insufficiency. The test does not differentiate between an obstructive ventilatory impairment and a severe restrictive defect. A positive result to the match test implies a diminution of the 1-second vital capacity to

*Mayo Clinic and Mayo Foundation: Section of Medicine.
**Mayo Clinic and Mayo Foundation: Section of Physiology.

less than about 1,500 ml[3] and of the maximal breathing capacity (MBC) to less than 40 liters/min. or 50% of the predicted MBC.[4] Olsen[5] suggested that the match test may identify not only patients who have maximal breathing capacities of 40 liters/min. or less but also those who have maximal midexpiratory flow rates of 0.6 liter/sec. or less.

Vitalor

A bellows apparatus, such as the McKesson Vitalor (Figure 2), can be employed in the office or on the hospital ward to obtain the total vital capacity (VC), timed vital capacity or forced expiratory volume (FEV), and maximal expiratory flow rate (MEFR).[6,7] A nose clamp may be used to prevent escape of air. The patient inhales as deeply as possible. When the maximal inspiration is attained, an electric switch button on the instrument is closed to activate the recorder, and the patient is asked to exhale completely through the disposable mouthpiece into the bellows. This measures the total VC, provided it does not exceed the bellows' capacity of 4.8 liters. The timed VC is performed similarly with the patient making a forced, maximally rapid expiration after a maximal inspiration. The record showing several measurements is illustrated in Figure 3. The total volume expired represents the vital capacity, which may be compared with predicted normal values. Also shown is the volume expired in the first second, which normally represents about 80 to 85% of the forced VC.[8] The MEFR is calculated from that portion of the expiration curve beginning at 200 ml. and ending at 1,200 ml. The time required for the subject to exhale this liter of air is recorded. The average slope of this curve, properly located on the chart, indicates the MEFR, which normally exceeds 300 liters/min.[9,10] The record is also suitable for another measurement which determines the average flow rate of the middle 50% of the VC; this is designated as maximal midexpiratory flow rate and is expressed in liters per second.[11]

Impairment of ventilation is classified into three types: restrictive, obstructive, and combined. Restrictive ventilatory insufficiency (e.g., pulmonary fibrosis, pleural effusion, and resection of lung tissue) is indicated by reduction of the total VC but without slowing of expiratory air flow. Obstructive ventilatory insufficiency (emphysema, etc.) is indicated by time-volume relationships. The volume that is expired by maximal effort in the first second may be expressed in liters or as a percentage of the vital capacity performed. This is a valuable test in patients who have obstructive pulmonary disease and can readily be determined by the Vitalor. Figure 4 shows the expiratory pattern in chronic obstructive pulmonary disease. With advanced impairment, the total VC is reduced, but not as greatly as the expiratory flow rate. This is shown by the reduction in the volume expired in the first second (FEV_1) and its relation to the total VC, as well as in the midexpiratory flow rate.

Relation of Tests to Results

This report presents the relation of these simpler ventilatory tests to results obtained with more extensive established pulmonary function tests usually done on the same day.



Fig. 1—Position for match test. Match is held 6 inches from wide open mouth, and patient forcefully exhales after deep inspiration.



Fig. 2—Use of bellows apparatus (Vitalor). Results are recorded on graph at top of instrument.

The tests were conducted on 50 patients who had clinical evidence of pulmonary disease, usually of the chronic obstructive type, of varying degrees of severity. The group included 41 men and nine women, whose ages varied from 28 to 74 years (mean, 55 years).

Table 1 summarizes the results of the match test and spirometric tests measured with the Vitalor. No patient with FEV of less than 1.5 liters passed the match test. However, seven patients with FEV of greater than 1.5 liters failed. No patient with MEFR of less than 100 liters/min. passed, but seven with MEFR of 100 liters/min. or more failed. No patient with MMF of 0.6 liter/sec. or less passed, but four with values of 1.3 liters/sec. or more failed. It is possible that the patients with relatively good ventilatory tests who failed the match test might have passed with further testing efforts.

Table 2 presents results of other pulmonary function tests. Only one of 26 patients with maximal breathing capacity values of less than 60 liters/min. passed, but four with values of 90 liters/min. or more failed. The ratio of residual volume to total lung capacity (RV/TC), long used in evaluating severity of obstructive pulmonary disease, is associated with a progressive incidence of failure as RV/TC increases. Only one of 25 patients with RV/TC of 50% or greater passed, but three with RV/TC of 39% or less failed. All patients with obstructive disease who passed the match test maintained a normal level of arterial oxygen saturation during moderate exercise. The one patient who passed the match test, but in whom arterial desaturation developed, had diffuse pulmonary fibrosis without impaired expiratory flow.

These results agree with reports of Snider and associates[3] who found that passing the

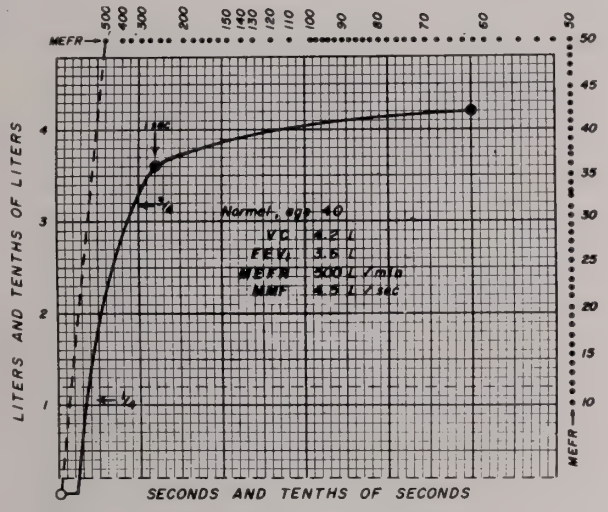


Fig. 3—Normal record from Vitalor.

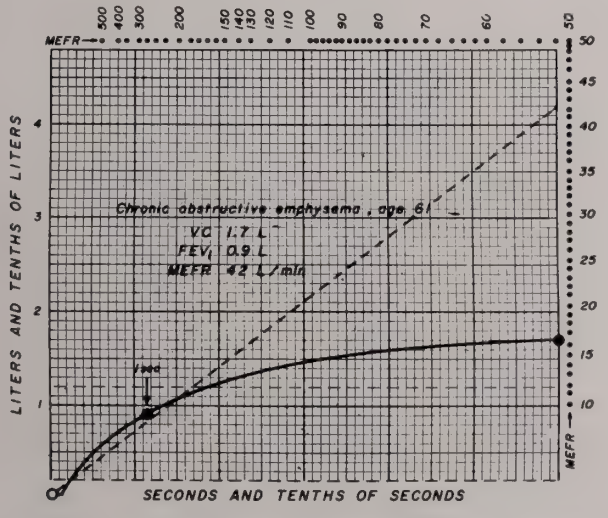


Fig. 4—Abnormal record in case of chronic obstructive emphysema.

TABLE 1

Results of the Match Test and Other Expiratory Flow Measurements

Value of spirometric test	Match test	
	Passed*	Failed*
FEV_1, liters		
0 to 0.49	....	3
0.5 to 0.99	....	11
1.0 to 1.49	....	18
1.5 to 1.99	5	4
2.0+	6	3
MEFR, liters/min.		
0 to 49	....	16
50 to 99	....	16
100 to 149	4	4
150 to 199	2	2
200+	5	1
MMF, liters/sec.		
0 to 0.6	....	22
0.7 to 1.2	2	12
1.3 to 1.8	5	1
1.9 to 2.4	1	1
2.5+	3	2

* Number of patients.

match test implies that the FEV_1 is likely to exceed about 1.5 liters. Barry [12] similarly reported that passing indicates the $FEV_{0.75}$ to exceed 1.0 liter. We observed three patients who failed the match test despite values exceeding 2.0 liters. Also, passing the match test indicates MEFR to exceed 100 liters/min. and MMF to exceed 0.6 liter/sec. Olsen[5] related MMF to the match test using a shorter mouth-to-match distance (three inches); practically all failures were associated with MMF values of 0.6 liter/sec. or less; but at this distance many patients passed. Our results with MBC are similar to those of Snider and associates and indicate that passing the match test implies MBC values of 60 liters/min. or more; however, failures occurred above this level.

TABLE 2
Results of the Match Test and Other Pulmonary Function Tests

Values of other tests	Match test	
	Passed*	Failed*
Maximal breathing capacity, liters/min.		
0 to 29	....	6
30 to 59	1	19
60 to 89	3	10
90 to 119	6	4
120+	1	....
Residual volume / total capacity x 100, %		
20 to 29	2	....
30 to 39	5	3
40 to 49	3	12
50 to 59	1	14
60+	....	10
Arterial O_2 saturation (exercise), %		
94 or more	10	25
93 or less	1**	12

*Number of patients.
**Diffuse fibrosis.

To assess the utility of the tests obtained with the Vitalor (VC, FEV, MMF, MEFR) relative to more complete tests, including the MBC and RV/TC ratio, the severity of obstructive impairment was graded separately for each group of measurements on a scale of 0 to 4, with 0 representing the least and 4 the greatest degree of impairment. The mean score (2.9) was the same for the two methods. In 60% of the patients the scores were the same by the two methods; differences of 1 scale unit occurred in the other 40%, with greater severity being indicated by Vitalor in 20% and by the extended tests in 20% (Table 3).

TABLE 3
Grading of Impairment by Few or More Tests

Grade of severity	Tests*	
	Few	More
0	2	3
1	4	5
2	11	5
3	11	17
4	22	20

*Number of patients.

Summary

Fifty adult patients having chronic pulmonary disease, mainly of the obstructive type, were studied by the match test, with the Vitalor apparatus, and with more complete tests of pulmonary function. Ability to pass the match test was associated with values of FEV_1 greater than 1.5 liters, MEFR greater than 100 liters/min., MMF greater than 0.6 liter/sec., and MBC greater than 60 liters/min. Some failures were observed above all the levels listed. Arterial oxygen unsaturation during exercise by patients with obstructive disease was observed only in some of the patients who failed the match test. Similar gradation of severity of impairment was indicated by both Vitalor and more extensive tests.

In the physician's office, early detection of obstructive pulmonary disease, periodic evaluations, and assessment of operative risk are facilitated by relatively simple pulmonary function tests, particularly if the forced or timed vital capacity is recorded. These are useful adjuncts to the history, physical examination, and roentgenogram of the chest.

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1. Mittman, C.: Assessment of Operative Risk in Thoracic Surgery. Amer Rev Resp Dis 84:197, 1961.
2. Stonehill, R. B., and Reed, J. E.: Simplified Pulmonary Physiology for Office Practice. Ann Intern Med 53:106, 1960.
3-12. May be secured from the author or the reprints.

Knock-Knock

Opportunity doesn't knock at the door—she answers when you *knock.—Walter L. Hays*

|| D. Pneumoniae

Increased Resistance to Oxacillin and Cloxacillin

THOMAS C. SHOPE, M.D.*
PAUL G. QUIE, M.D.**
Minneapolis, Minnesota

The isolation of *D. pneumoniae* (type 9) with increased resistance to oxacillin and cloxacillin from the blood of a patient during treatment with oxacillin is the subject of this report.

Case Report

A nine-year-old white female was admitted to the University of Minnesota Hospitals for the twelfth time on January 9, 1966. She was hospitalized for repair of an esophageal stricture present since March 1965. Starting at age 30 months this Caucasian child was repeatedly hospitalized because of recurrent staphylococcal infections, manifested primarily by furunculosis and pneumonia. Chronic pulmonary disease and bronchiectasis had developed by four years of age. At five years hypergammaglobulinemia with a normal distribution of immunoglobulins was found and there was a normal antibody response to immunization with typhoid and polio antigens. Serum antibodies to staphylococcal alpha hemolysin were present in low titer, with no detectable antibody to staphylokinase. The phagocytic and bactericidal capacity of polymorphonuclear leukocytes were found to be comparable to normal controls.[1]

In February 1965 there developed diffuse vasculitis with necrosis and eventual auto-amputation of three digits on each hand. Progressive stricture of the esophagus developed during this episode of vasculitis. No bacteria were recovered from blood, urine or exudate fluid.

Treatment for extended periods with either oxacillin or methacillin had been initiated in 1961 and the patient had received oxacillin daily for approximately 10 months before her final hospital admission. Oxacillin (150 mg/kg/day orally) was continued in the hospital. She was afebrile until eight days after admission when fever of 104° suddenly developed. Pneumococci were cultured from the blood. A sputum culture revealed *P. aeruginosa.* Penicillin (12,000,000 units/day I.V.) was given, and 18 hours after start of this therapy the patient was afebrile. A cervical esophagostomy was performed four weeks after admission; however, pneumonia, atelectasis and cardiac failure developed postoperatively and she expired seven days after surgery. Post-mortem blood cultures were sterile.

The pneumococcus isolated from the blood was type 9. Repeated tube dilution sensitivities with inoculum of approximately 1 x 10^6 bacteria per ml. showed resistance of the organisms to oxacillin at concentrations ranging from 3.1 μg/ml.-5 μg/ml. This degree of resistance was demonstrable after at least five subcultures of the organism on nutrient agar plates. Additional sensitivity

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studies (courtesy J. H. Lennon, Bristol Laboratories, Syracuse, New York) showed that in addition to increased resistance to oxacillin there was resistance to cloxacillin at 6.25 μg/ml. but sensitivity to penicillin G at 0.39 μg/ml.

Discussion

In 1963 reports appeared describing tetracycline-resistant pneumococcal strains.[2,3,4] Presently 18 isolates with resistance to this antibiotic have been recorded.[5,6] All but one of these strains were of pulmonary origin in patients with chronic bronchitis and many appeared in patients who had been treated with tetracycline for more than 12 days.[3,4] In addition to tetracycline resistance *D. pneumoniae* strains resistant to erythromycin and lincomycin have recently been reported.[7]

The sensitivity of clinical isolates *D. pneumoniae* to oxacillin has been reported to range from 0.04 to 0.8 μg/ml. Methicillin sensitivity ranged from 0.1 to 1.6 μg/ml. and sensitivity to penicillin G was 0.1 μg/ml.[8] It has been suggested that, since the minimal inhibitory concentrations of oxacillin, cloxacillin and nafcillin against non-penicillinase-producing gram-positive organisms are so relatively close to those of penicillin G, one of these agents could be used as initial therapy in all severe gram-positive coccal infections.[9] The recovery of a strain of *D. pneumoniae* with increased resistance to oxacillin and cloxacillin from a patient on oxacillin therapy indicates the need for determination of antibiotic sensitivity of pneumococci isolated from patients receiving antibiotics.

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Recourse to History

Hippocrates made his mental cases drink human blood. He maintained that the blood of sound persons had a sound soul.

Some 400 years ago a theory was circulated that a man would become brave and generous if he takes blood from one who possesses either of these qualities.

Marie de' Medici, who lived in the early 17th century and was known for her cruelty, dreaded the prospect of old age and its attendant ailments. One of her court physicians suggested that she drink human blood.

At the close of the 15th century Pope Innocent VIII was treated with a potion also prepared from human blood.

Naturally, all these instances cost the lives of those whose blood was taken for the various potions. But they show that the idea of utilizing the healing powers of blood has occupied men's minds through the centuries.

The first blood transfusion from man to man was made early in the 19th century. It was made to a patient suffering from stomach cancer—a patient who in that day was doomed to die. . . . Andre Blondel, the physician who treated him, decided to try a blood transfusion. He had read about its prospects in medical journals, and had even tried it himself on animals. Though the journals condemned the idea as contrary to age-old medical precepts, the physician reasoned that his patient had nothing to lose.

The dying man was transferred to a hospital. One of the attendants agreed to give some of his blood. The transfusion was successful. A day passed, a second, a third, and there were no ill effects. The patient lived longer.

That was the first blood transfusion in history. It dates back to 1818.*

---

*L. Fridland, M.D.: The Achievement of Soviet Medicine, 1961 edited and translated from the Russian by W. Horsley Gantt, M.D.



Let's be specific about Campbell's Soups... and *reducing diets*



There are more than 30 million people in America who are overweight. During the next year, you probably will see more than 1,000 of them in your own practice.

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Campbell has prepared a sensible plan for weight control based on ordinary eating patterns. The plan consists of a patient instruction booklet and a set of menus which provide approximately 1,200 calories daily. The menus are balanced to provide the minimum daily requirements of nutrients.



To obtain a supply for your office write to:
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Each tablet and each 5 cc. of liquid contains:
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(Warning: may be habit forming)
atropine sulfate . . . . . 0.025 mg.

Halts Diarrhea Promptly

in children with . . . Gastroenteritis ▪ Spastic bowel
Influenza-like infections ▪ Antibiotic-induced diarrhea

Lomotil helps get children with diarrhea off toast and tea and back to normal diets and normal activity with gratifying dispatch. ▪ Lomotil lowers intestinal motility and permits absorption of excess fluid. This usually controls diarrhea promptly. ▪ Moreover, lowered intestinal motility achieved with Lomotil often relieves the abdominal cramps and discomfort so distressing to children.

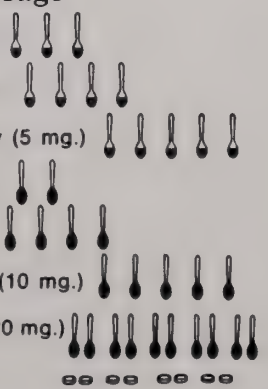
Precautions: Lomotil is a Federally exempt narcotic preparation of very low addictive potential. Recommended dosages should not be exceeded, and medication should be kept out of reach of children. Should accidental overdosage occur signs may include severe respiratory depression, flushing, lethargy or coma, hypotonic reflexes, nystagmus, pinpoint pupils, tachycardia; continuous observation is recommended. Lomotil should be used with caution in patients with impaired liver function or those taking addicting drugs or barbiturates.

Side Effects: Side effects are relatively uncommon but among those reported are gastrointestinal irritation, sedation, dizziness, cutaneous manifestations, restlessness, insomnia, numbness of the extremities, headache, blurring of vision, swelling of the gums, euphoria, depression and general malaise.

Dosage: The recommended initial daily dosages, given in divided doses until diarrhea is controlled, are:

Children: Total Daily Dosage

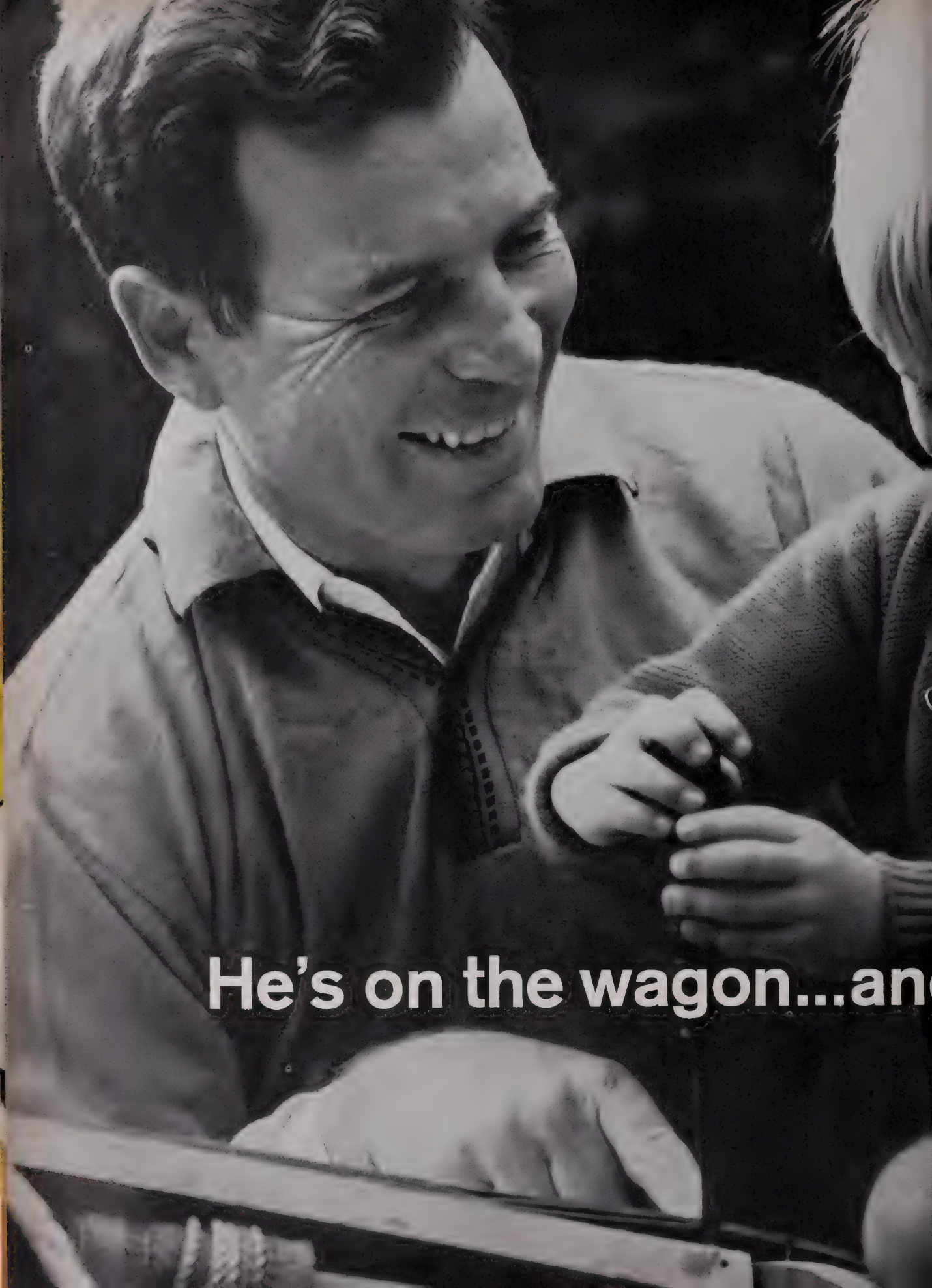
3-6 mo. . .½ tsp.* t.i.d. (3 mg.)
6-12 mo. .½ tsp. q.i.d. (4 mg.)
1-2 yr. . . .½ tsp. 5 times daily (5 mg.)
2-5 yr. . . .1 tsp. t.i.d. (6 mg.)
5-8 yr. . . .1 tsp. q.i.d. (8 mg.)
8-12 yr. . .1 tsp. 5 times daily (10 mg.)
Adults: . .2 tsp. 5 times daily (20 mg.)
or 2 tablets q.i.d.



*Based on 4 cc. per teaspoonful.

Maintenance dosage may be as low as one-fourth the initial daily dosage.

SEARLE *Research in the Service of Medicine*


He's on the wagon...an

How well does Vistaril relieve the symptoms that plague an alcoholic during the recovery period? Doctors Knott and Beard of the Alcoholic Rehabilitation Unit, Tennessee Psychiatric Hospital and Institute, recently conducted a double-blind study comparing Vistaril and another well-established antianxiety agent with placebo in 60 chronic alcoholic patients.[1]

The investigators conclude: "It was the opinion of the staff that hydroxyzine was generally more effective than chlordiazepoxide, for the following reasons: hydroxyzine was equally if not more effective in reducing anxiety and tension and it produced less daytime sedation...."[1] (See results on succeeding pages.)

Here is new evidence that Vistaril can ease tension, allay anxiety in chronic, hospitalized alcoholic patients. *But you might also choose Vistaril for what it doesn't do.* Although not evaluated in this study, Vistaril is reported to be non-euphoriant, and its low toxicity makes it relatively safe. Best of all, Vistaril is non-habituating. To date, after more than ten years of clinical use, there have been no reports of dependency in patients receiving Vistaril.

With Vistaril, it is as easy to stop therapy as it is to start.

Vistaril®
(HYDROXYZINE PAMOATE)

the study: Sixty chronic alcoholic patients were hospitalized and randomly assigned to one of three oral double-blind treatment regimens for three weeks. Twenty patients received hydroxyzine (Vistaril®), 100 mg. q.i.d.; twenty others were given chlordiazepoxide, 25 mg. q.i.d.; and the remaining twenty received placebo capsules q.i.d. The capsule code was not made known until after completion of the study and analysis of the data. Response was measured with a modification of the Brief Psychiatric Rating Scale as originally outlined by Overall and Gorham.* Subjects were rated daily by trained staff members.

SYMPTOM RATING KEY

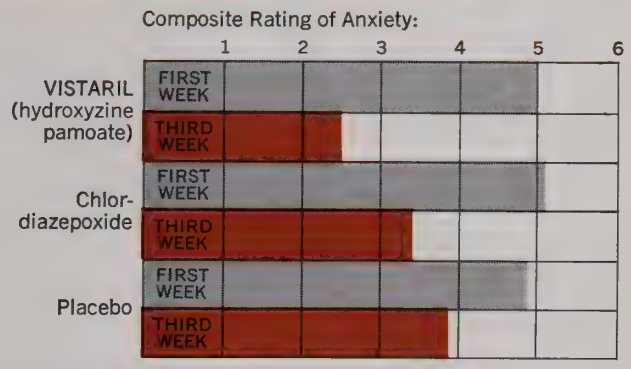
1=Not Present	4=Moderately Severe
2=Mild	5=Severe
3=Moderate	6=Extremely Severe

The figures which are given below represent the composite conclusions of the staff based on daily ratings during initial and final weeks of the study.

*Psychological Reports 10:799, 1962

the results' DURING FIRST WEEK DURING THIRD WEEK

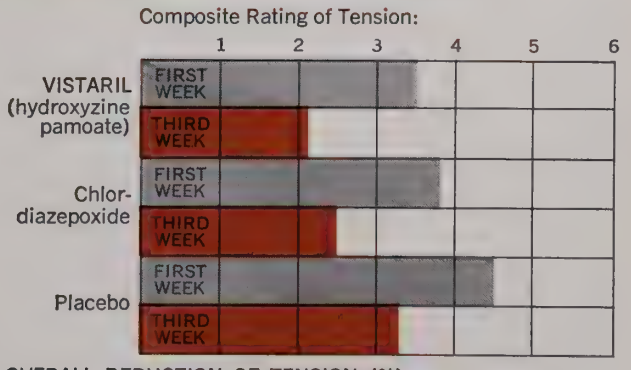
Anxiety reduced with Vistaril



OVERALL REDUCTION OF ANXIETY (%)

VISTARIL (hydroxyzine pamoate)	Chlordiazepoxide	Placebo
50%	33%	20%

Tension eased with Vistaril



OVERALL REDUCTION OF TENSION (%)

VISTARIL (hydroxyzine pamoate)	Chlordiazepoxide	Placebo
40%	34%	27%

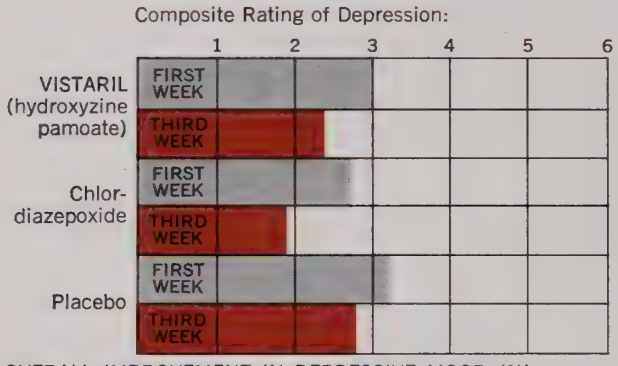
PLEASE SEE LAST PAGE FOR PRESCRIBING INFORMATION

In Alcoholism...

"Both hydroxyzine and chlordiazepoxide were generally more effective than the placebo. In some aspects, hydroxyzine was superior to chlordiazepoxide, which is currently the most frequently used psychotropic drug in the management of alcoholism."[1]

DURING FIRST WEEK DURING THIRD WEEK

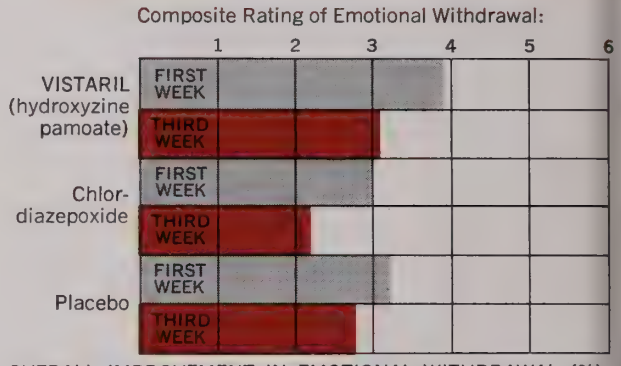
Depressive mood improved with chlordiazepoxide



OVERALL IMPROVEMENT IN DEPRESSIVE MOOD (%)

VISTARIL (hydroxyzine pamoate) 20% | Chlordiazepoxide 30% | Placebo 13%

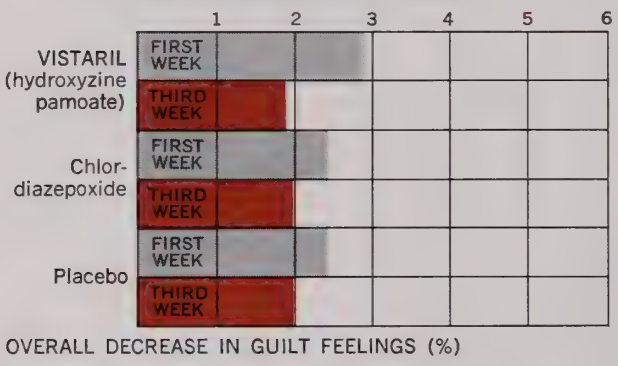
Emotional withdrawal counteracted with chlordiazepoxide



OVERALL IMPROVEMENT IN EMOTIONAL WITHDRAWAL (%)

VISTARIL (hydroxyzine pamoate) 21% | Chlordiazepoxide 27% | Placebo 13%

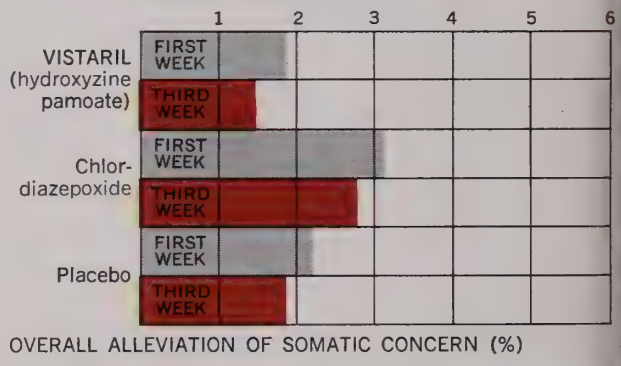
Guilt feelings allayed with Vistaril



OVERALL DECREASE IN GUILT FEELINGS (%)

VISTARIL (hydroxyzine pamoate) 34% | Chlordiazepoxide 17% | Placebo 17%

Somatic concern alleviated to minor degree in each group



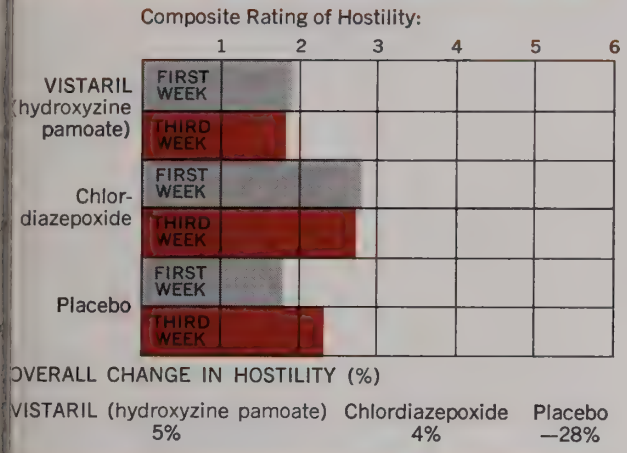
OVERALL ALLEVIATION OF SOMATIC CONCERN (%)

VISTARIL (hydroxyzine pamoate) 17% | Chlordiazepoxide 13% | Placebo 14%

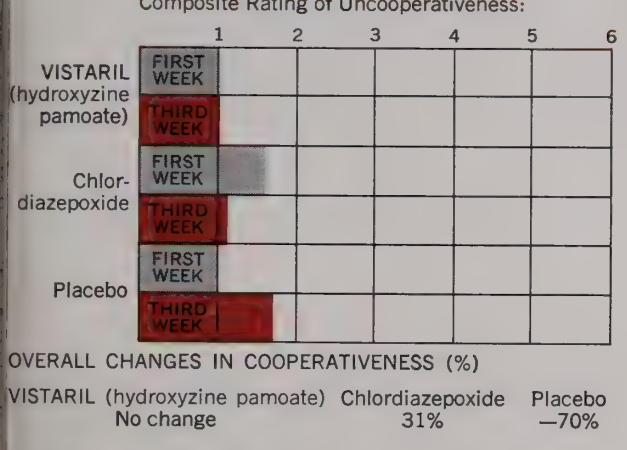
Less drowsiness with Vistaril

	Drowsiness	Dizziness	Mouth Dryness	Increased Motor Activity	Ataxia	Nausea	Comments
VISTARIL (hydroxyzine pamoate)	6 patients (mild)	3 patients (mild)	2 patients (moderate)	—	—	—	Side Effects Not Treated
Chlor-diazepoxide	10 patients (severe in 6)	4 patients (mild)	—	1 patient (moderately severe in first week but gradually subsided)	—	—	Side Effects Not Treated
Placebo	2 patients (mild)	2 patients (mild)	—	—	1 patient (mild)	2 patients (mild)	Side Effects Not Treated

Increase in hostility minimized with Vistaril and chlordiazepoxide



Cooperativeness not a significant problem



In Alcoholism...

Vistaril®

(HYDROXYZINE PAMOATE)

BRIEF SUMMARY

Contraindications: Hypersensitivity to hydroxyzine. The parenteral solution, for intramuscular or intravenous use, *must not* be injected subcutaneously or intra-arterially.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate. Until adequate data are available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.

Precautions: Hydroxyzine may potentiate the action of central nervous system depressants such as narcotics and barbiturates. In conjunctive use, dosage for these drugs should be decreased, as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. Hydroxyzine parenteral solution for intramuscular use should be injected well within the body of a relatively large muscle. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. In children, preferably the mid-lateral muscle of the thigh. In infants and small children the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in order to minimize the possibility of damage to the sciatic nerve. The deltoid area should be used only if well developed, such as in certain adults and older children, and only with caution to avoid radial nerve injury. Injections should not be made in the lower and middle thirds of the upper arm. Aspiration should be done to help avoid intravascular injection. On reported intravenous injection a few instances of digital gangrene have occurred distal to the injection site, considered to be due to inadvertent intra-arterial injection or possibly periarterial extravasation. Therefore, particular caution (aspiration and site injection) should be observed to insure injection only into intact veins; avoid either intra-arterial injection or extravasation. Intravenous administration should be accomplished slowly, no faster than 25 mg. per minute, and not to exceed 100 mg. in any single dose. In order to avoid possible adverse effects it is recommended that hydroxyzine parenteral solution be diluted to at least 50 cc. with sterile normal saline and administered over a period of four minutes or more, preferably into the tubing of a running intravenous infusion.

Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.

When this product is given intravenously undiluted, minimal amounts of intravascular hemolysis occur at the site of injection. Giving the maximum recommended intravenous dose (100 mg.) to adults results in immediate transient hemolysis with the liberation of a total of 2-3 grams of hemoglobin, which, in some individuals, can cause small amounts of hemoglobinuria. This compares with the normal red cell destruction from which approximately 8 Gm. of hemoglobin are liberated every 24 hours. If the hydroxyzine is diluted with 50 cc. of normal saline and given during a period of four minutes or more, this phenomenon does not occur.

Supply: Vistaril (hydroxyzine pamoate) Capsules: Equivalent to 25 mg., 50 mg., 100 mg. hydroxyzine HCl. Vistaril (hydroxyzine pamoate) Oral Suspension: Equivalent to 25 mg. hydroxyzine HCl per 5 cc. teaspoonful. Vistaril (hydroxyzine HCl) Parenteral Solution: 25 mg./cc.—10 cc. vial and 50 mg./cc.—2 cc. and 10 cc. vial; Isoject,® 25 and 50 mg. per cc., 1 cc. per unit.

More detailed professional information available on request.

Reference: 1. Knott, D.H. and Beard, J.D.: GP 36:118, September, 1967.

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Prescribing Information: Composition: Each white, beveled, compressed tablet contains: Quinine Sulfate 260 mg. and Aminophylline 195 mg. **Contraindication:** QUINAMM is contraindicated in pregnancy because of its quinine content. **Precautions:** Aminophylline may produce intestinal cramps in some instances, and quinine may produce symptoms of cinchonism, such as tinnitus, dizziness, and gastrointestinal disturbance. Discontinue use if ringing in the ears, deafness, skin rash, or visual disturbances occur. **Dosage:** One tablet upon retiring. Where necessary, dosage may be increased to one tablet following the evening meal and one tablet upon retiring. **Supplied:** Bottles of 100 and 500 tablets.

References: 1. Shuman, C.: Am. J. Med. Sci., 225:54, 1953. 2. Perchuk, E., et al.: Angiology, 12:102, 1961. 3. Rawls, W., et al.: Med. Times, 87:818, 1959.

6/67 Q-706A



Editorials

Porphyria*

THE DRAMATIC effect of confirming the diagnosis of porphyria by the finding of abnormal amounts of porphyrins or porphyrin precursors, or both, in the blood, urine, or stool has increased the clinical interest in this relatively rare metabolic disorder. The patient with acute intermittent porphyria who presents variations in the triad of classic findings consisting of recurrent colicky abdominal pain, psychic disturbances, and peripheral neuropathies has, at times, confounded even the most astute internist, neurologist, or surgeon. Unusual combinations of findings occurring in the patient with acute intermittent porphyria, as reported by Shuman and Snively,[1] demonstrate the importance of considering altered porphyrin metabolism as being responsible for varied and unusual combinations of symptoms.

Dermatologists have long been interested in another form of the disease, namely porphyria cutanea tarda.[2] In this condition, various photosensitive or blistering dermatoses have been considered as causes of such reactions because the skin of the sun-exposed areas of the hands and forearms, face, and neck are readily susceptible to trauma and blistering. Among these dermatoses are included epidermolysis bullosa, hydroa aestivale,** bullous impetigo, erythema multiforme, and drug reactions.

Secondary changes, such as suffusion of the face and upper trunk, scleral injection, ulceration, scarring sclerosis, and hyperpigmentation of the skin, usually permit ready clinical diagnosis of porphyria cutanea tarda. At times, milia, hirsutism, and darkening of the hair, or all of these, add confirmatory evidence to the diagnosis. A degree of liver dysfunction is usually present.

Some drugs can precipitate or cause a recurrence of porphyria cutanea tarda, as they do acute intermittent porphyria. Estrogenic preparations have been known to precipitate flares of acute intermittent porphyria, and overt signs of porphyria cutanea tarda can be seen in a middle-aged man who is taking estrogens as a part of therapy for carcinoma of the prostate.[3] The antimalarial drugs, used as anti-inflammatory agents in some diseases (lupus erythematosus and arthritis), also may precipitate a flare of porphyria.[4] Hexachlorobenzene,[5] which had been used as an antifungal agent in the treatment of wheat sent to Turkey, precipitated a form of porphyria characterized by severe mutilation of the skin and hirsutism and was referred to as Turkish porphyria.

Griseofulvin, a drug now commonly used in the clinical management of superficial fungous infections of the skin, was recognized as altering the metabolism of porphyria in mice.[6] Later, this same alteration was noted in patients with porphyria who were given this drug,[7,8] at times with exacerbations of their symptoms.

The presumption in the drug-exacerbated

*Shuman H. W., and Snively, W. D., Jr.: Porphyria—Strange and Baffling Ailment. Minnesota Med. 50: *1463*, 1967.

**See Test Your Word Score Page 53.

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porphyrias is that in some manner these drugs interfere with the biosynthesis of heme, with the production of the porphyrin products characteristic of the particular clinical type of the disease. For example, Levere,[9] after the finding of increased levels of aminolevulinic acid synthesis in chemically induced hepatic porphyria, demonstrated increased levels of this same rate-limiting enzyme in a patient who had signs of porphyria cutanea tarda while receiving diethylstilbestrol.

As the details of porphyrin metabolism have become known, some diseases previously considered "idiopathic" are now recognized as being associated with altered porphyrin metabolism. These include solar urticaria,[10] eczema solare,[11] and hydroa aestivale,[12] all of which are associated with protoporphyrin.

Harold O. Perry, M.D.
Rochester, Minnesota

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Cesarean Hysterectomy

THERE HAS been controversy in recent years concerning the advisability of cesarean hysterectomy replacing cesarean section with tubal ligation for sterilization. Janes, Smith and Williams* elsewhere in this issue in a series of 25 cesarean hysterectomies have shown that significant complications occur. Excessive blood loss and bladder injury are the most frequently encountered. Bladder injury led directly to one death. It must be emphasized that seven hysterectomies were performed as life-saving procedures and five patients had malignant disease. Another two patients had impending intrauterine infection, and hysterectomy or extraperitoneal cesarean section may have been mandatory. In considering the role of cesarean hysterectomy for sterilization these 14 cases must be excluded.

Seven patients had uterine myomas or congenital anomalies and, although sterilization was a likely consideration in these cases, it was only the remaining four patients with defective uterine scars whose pelvic pathology would not present problems in the nonpregnant state. It is this small group which must be compared with cesarean section and tubal ligation. Nevertheless, the added risk of complications associated with removal of the normal uterus, although admittedly small, is probably not justified as an elective procedure even when balanced against the one to two percent probability of cancer of the cervix developing in the subsequent 50 years.[1]

The patient with pelvic pathology may have a definite indication for hysterectomy, but since cesarean section is frequently unscheduled, it is usually best to perform the definitive surgery at a later time when conditions are optimal.

Leon L. Adcock, M.D.
Minneapolis, Minnesota

*See page 17.

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Episodic Vertigo

In few conditions encountered in the practice of medicine is the etiologic diagnosis more difficult than that of episodic vertigo. Dr. Williams'* plea that we seek the specific cause for each case of episodic vertigo is of extreme importance for the success of the treatment, especially if one of the many surgical procedures is to be considered. Failure is certain if an unnecessary or inappropriate operation is performed. It follows that, in order to make an accurate diagnosis, every patient with episodic vertigo should have a thorough neuro-otologic examination with special attention to the history. Minimally, the tests should include audiography for pure-tone and speech discrimination, caloric vestibular tests (preferably by electronystagmography), and roentgenograms of the temporal bones. These examinations are relatively inexpensive and far less difficult to interpret than the electrocardiogram which is now routinely included in any thorough cardiac examination.

Should the vestibular and audiometric tests indicate a specific region of involvement, more extensive audiometric examination may be done. Intracranial disease likewise requires specific testing: for example, roentgenologic study with contrast medium for tumors of the cerebellopontine angle, cerebrospinal fluid electrophoresis for multiple sclerosis, electroencephalogram for temporal lobe brain abscess, or electronystagmography to detect directional preponderance for brain-stem viral encephalitis. A trial of anticoagulants may be the only way a diagnosis of basilar artery insufficiency may be confirmed; or a trial of diphenylhydantoin (Dilantin) to relieve the attacks of vertiginous epilepsy may be necessary.

As Dr. Williams points out, the most common cause of episodic vertigo seems to be a stimulus affecting the righting reflexes in the head or neck. We see such patients with cervical spondylitis, sprained cervical muscles, and cervical injury. Although we have no treatment which will immediately cure these disorders, symptomatic treatment to the neck and the use of antivertiginous drugs will often give relief.

With a careful analysis of every patient and the development of greater knowledge about the cause of vertigo, it is hoped that fewer patients will have a diagnosis of psychogenic vertigo or a nonspecific diagnosis, such as "Meniere's syndrome."

Jack L. Pulec, M.D.
Rochester, Minnesota

*Williams, Henry L.: The Episodic Vertigos. Minnesota Med 50:1008, 1967.

Communication Disorders in Children

"Deafness in Young Children" by John E. Bordley,* M.D., Professor of Otolaryngology at Johns Hopkins University School of Medicine, covers more than inability to hear. The broad concept of communication disorder, rather than the narrow concept of hearing disorder, should be considered when training or treating the child whose ability to communicate is delayed.

Hearing is an important part of communication, and indeed without hearing, the child develops verbal language skills only after much hard work by both the child himself and his teacher; and at best, these skills are limited in scope and are of poor quality. At the same time, factors other than deafness may contribute to the delayed development of language. These are mental retardation, brain damage, and some forms of aphasia. One can-

*Bordley, John E.: Deafness in Young Children. Minnesota Med 50:827, 1967.

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not assume that delayed language development is the result of any one of these factors, and the child who does not develop normal communication patterns should be studied in sufficient detail to determine which of the several possible defects is the cause of the delay. Only with such knowledge can an appropriate system of training or treatment be developed. Doctor Bordley's paper covers this field with clarity and comprehension. It should be of great value to all physicians who deal with children.

Kinsey M. Simonton, M.D.
Rochester, Minnesota

Neoplasia of the Parotid Gland*

PAROTIDECTOMY—EITHER subtotal or total—is the surgical procedure of choice in the management of tumors of the parotid gland. These lesions should not be enucleated or excised; and the facial nerve should be sacrificed, in part or totally, only when a malignant tumor involves the nerve or a portion of it.

Commonly the parotid gland was spoken of as a bilobar structure—a superficial lobe and a deep lobe connected by an isthmus, with the facial nerve going around the isthmus. However, Winsten and Ward** proved that the gland is a unilobar structure, with the facial nerve and its branches transgressing the gland and dividing it into a superficial part and a deep part.

The facial nerve is very consistent in its relationship to adjacent anatomic structures as it leaves the styloid foramen and projects beyond the parotid gland at its periphery. The safest surgical approach to the facial nerve is for the main trunk to be identified immediately medial and deep to the mastoid process in the substance of parotid gland. The dissection can then be carried peripherally. To identify peripheral branches and carry the dissection proximally is time consuming and hazardous.

If function of the facial muscle is to be preserved (when indicated) and the results of treatment are to be the best for the individual patient, parotid surgery should be done only by surgeons who are well trained and experienced in the techniques of parotidectomy.

Oliver H. Beahrs, M.D.
Rochester, Minnesota

*Lathrop, F. D.: Neoplasia of the Parotid Gland. Minnesota Med 50:999, 1967.
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Test Your Word Score

Placenta percreta—*placenta accreta with invasion of the uterine wall to its serosal surface* (page 18).

Trichomonas vaginalis—*a genus of parasitic protozoa that cause a refractory discharge* (page 28).

Hydroa aestivale—*a skin disease characterized by vesicles upon patches of erythema* (page 47).

Seminoma—*a tumor derived from germinal epithelium which has failed to differentiate into either male or female-type cells* (page 73).

Avicenna—*Arab physician* (980-1037) (page 76).

Anisocoria—*pupils of unequal size* (page 79).

Polyhedral—*having many sides* (page 80).

Lumbrici—*intestinal worms* (page 116).

Res ipsa loquitur—*literally, the thing speaks for itself* (page 122).

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I was happy to hear that you had selected some quotes from my book, "Birth Control and Conscience," to appear in the Book Review Section* of MINNESOTA MEDICINE.

In recent years I have realized that (figuratively speaking) the government is watering the weeds in the garden of human life, and is thereby aiding these weeds to multiply as never before. Since the weeds tend to crowd out the useful plants, the situation has some resemblance to a cancer.

Public opinion is encouraging the multiplication of these human weeds on the basis of conscientious good intentions which favor unconditional charity to those who are hereditarily weak or weak-minded. I, of course, favor help to these people provided they do not pass their heredity on to future generations in excessive amounts.

M. H. Mothersill, M.D.
Minneapolis, Minnesota

*See Minnesota Med 50:1911, 1967.

Without doubt, Medicare, used properly, can benefit the elderly indigent; but so can the Kerr-Mills Act. Now that Medicare is a law, we must deal with the future as well as with the present. Of course, no one can foretell the future; however, not only the cornerstone, but also the entire foundation has been laid to project into the future many possible and highly probable provisions of this act.

Many proponents of Medicare feel that dealing with the fiscal intermediary is analogous to dealing with the local facility. Little do they realize that projected into the future is the provision that every medical and dental office will be required to submit all its bills to the fiscal intermediary. We shall have no choice!

How will our government enforce this provision? Our hospitals are now billing the fiscal intermediary; many staffed M.D.s are doing likewise. The government's next step will be to issue an ultimatum to our hospitals to the effect that the government will not allow the fiscal intermediary to issue funds to the hospitals, unless all of the M.D.s on the staff will accept assignment. This has already been programmed for a scheduled release date!

Now, you may say, "What's so bad about that? We are guaranteed 80% of our fees." This is correct; but please note that "fees" is the key word. What are fees? Are they ordinary and customary? They will be, up to a point. When this point has been reached our beneficent government will say, "Look, boys, your fees are not realistic, and we shall therefore determine what shall be a customary fee." We all know that prior to the inception of Medicare our welfare fees were extremely archaic. Are we going to regress to that era now—especially in view of the greater expansion of our present medical practices? Will it also be mandatory that we use generic medicine,

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some of which we have seen quite intact in the stools of our patients because of non-absorption?

Never before in the entire history of our nation did a bill invoke so much oppositional mail as did the Medicare bill. Nevertheless, this bill was inaugurated with great fanfare. Statements bordering on prevarication were released to the press. Propaganda such as we have never before seen now accompanies this act as it mushrooms like an atomic bomb. This law, like an atomic bomb. will encompass, and engulf, every individual in the medical profession.

Thus far there has not been an analytical statement of the cost or of the "benefit" of Medicare. From published literature we can quite safely assume that what Medicare recipients receive is basically incommensurate with their contributions.

In summation: the entire medical profession will be subjugated to governmental directives, procedures, reams of paper work and red tape unless we protest, not only as a group, but also as individuals. Protest to your county, state, and national academies as well as your county, state, and national representatives. In the case of welfare recipients, let the governmental agencies collect solely from each other. Let us keep our direct billing. As far as our regular Medicare patients are concerned, I believe you will find most of them completely honest; the elderly who come to our Clinic are very conscientious about paying us and do not want us to wait until they receive government remuneration. These people directly oppose Medicare but do not know what they can do about it. Advise them to write to their legislators and congressmen. Tell them also to write to the governor of their state.

Let's make this a campaign which will again give the people of this nation a voice in their government.

Stephan H. Earl, M.D.
Minneapolis, Minnesota

Cults and Quackeries

Of all the nations of the world, the United States is most afflicted by its healers. Besides those holding the degree M.D., signifying doctor of medicine and, nowadays, some seven years of study following high school graduation, a host of queer practitioners pervade the medical field. . . . Cult follows cult and quackery succeeds quackery, frequently with amazing rapidity. . . . A complete picture of the farcical scene would require endless research. The United States unquestionably bears the palm in every class so far as healing cults are concerned.

A cult is "excessive devotion to some person, idea, or thing, especially when pursued as an intellectual fad by a body of enthusiastic, self-constituted admirers." As applied particularly to medicine, a "sectarian" is one who in his practice follows a dogma, tenet, or principle, based on the authority of its promulgator to the exclusion of demonstration and experience.

The cults may be classified easily into mental healing cults, mechanical cults, electric cults, nature cults and similar divisions, since they adhere definitely to such single devices. Other cults may be classified as merely non-medical, since they deprecate the use of medicaments.

The complacency with which cultist leaders dispose of the fundamental facts of science in promoting their views may be taken as sound evidence of their essential eccentricities.*

---

*Morris Fishbein, M.D.: The New Medical Follies 1927.

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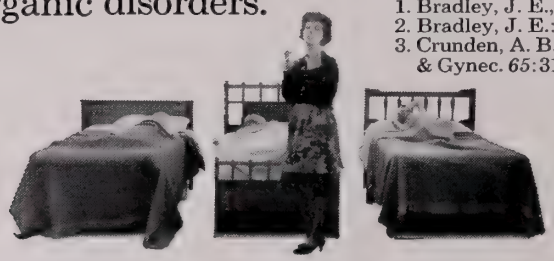
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Post Seasons Greetings

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Each year when the frost is off the pumpkin and the last trixertreat has been served for dessert, I sit down and write an inventory of family achievement. I take it to the printshop and have several hundred copies knocked out and then, with a sense of accomplishment and Christmas spirit, I send these letters to all points east and west. This is our family's Christmas Letter. After checking the galley proofs of our 1967 letter, and being a veteran of some ten years in my family's service, I decided that I had arrived at a point where I might be of aid as an instructor to individuals who will be entrusted with the task of composing their family's 1968 Letters.

As most of you are aware, the Christmas Letter is a relative newcomer on the scene of American letters. This hastily-written, carbon-smudged greeting captured the fancy of millions of us who saw in it the very medium for conveying to our distant friends not only that we lived but that we lived darned well and deservedly so.

The goal of the Christmas Letter author should be to set up his family as a tightly-knit group of well-adjusted, forward-thinking, public-spirited overachievers, moving with the sure-footedness of a Grand-Canyon mule from December to December.

Some cardinal points to remember are that honesty is often brutality, no one loves a failure, and "weep and you weep alone." One should strive for modesty and good taste in exposition: not, "John had a whale of a year; it looks as if we'll clear fifty grand!" but, "John has really worked much, much too hard."

When selecting which of the many accomplishments and honors to stress, it is well to bear in mind that some attainments rate higher than others in affecting a really fine family image. They could be listed roughly in the order of importance:

1. Fulbright Scholarships
2. Students obtaining admission to the college of their choice.
3. American Fields Scholars: (Always referred to as AFS Students) "Mary had a most meaningful summer as an AFS student in Yucatan."
4. Some connection with the diplomatic service or an occupation with an international flavor: "Marge was just a teeny bit lonely as the family kept the home fires burning while Roswell was in New Delhi on the President's Survey of Far Eastern Economics and Cultural Developments in the Plumber's Helpers Market."
5. A new step up for the bread-winner: "Weldon has really been burning the candle at both ends since being made VP at International last April—you wouldn't believe the mess he inherited."
6. A European trip: "This time we rented a car and just loafed our way along seeing the things that we really wanted to see—the Basque country, the little English villages, Irish pubs—we arrived in Donegal just three days after Jackie had been there."
7. A wedding: "Of course they will live in an apartment until Spencer gets his Ph.D., but that's all to the good, since Iris will be writing her thesis and won't have time yet for housekeeping in the grand manner."



"All Interns are Alike"

It stands to reason. They all go through the same training; they all have to pass the same tests; they all have to measure up to the same standards; they all are underpaid, too. Therefore, all interns are alike.

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So next time you hear someone say that all aspirin tablets are alike, you can say, with confidence, that it just isn't so.

You might also say that all interns aren't alike, either.



8. New baby: "Honestly, we would never have believed what an utter joy it could be."
9. Skiing trips: "We feel that the family never actually got to know each other before—the doctor says that Morty's cast can come off on the 5th day of July."
10. Self-improvement courses: "Emily will be our spokesman when we get to Guadalajara. The instructor says he has never seen anyone with such a flare for languages."
11. Community Service: "Of course it's just plain hard work, but Harold can be justly proud that the Fifth District went over the top months before any other."

That should be a fair sampling.

Life being what it is, however, perhaps the greatest effort the Christmas Letter author will have to exert will lie in the area of what I call "interpretation." So I will set forth here some representative facts and their constructive interpretation.

Fact	Interpretation
Kevin is a Hippie.	Kevin, our young individualist, is a student at Berkeley. He is majoring in Political Science and Chinese Lute Playing. His professors feel that he shows marked freedom of thought and expression.
Roger did not get the Fulbright hinted at in last year's Christmas Letter.	Roger rather surprised us with his maturity. He feels that nothing is to be gained from an Ivory Tower attitude towards Education. He has very wisely accepted a position as head of the History Department at Podunk Junior Elementary School.
Mother did not win the School Board Election.	Even before the returns were counted we held a family council and unanimously decided that regardless of the outcome Mother's place is in the home. We feel that all too many wives and mothers are away from home during these invaluable formative years.
Junior flunked sixth grade.	We decided to hold Junior back a year. The school counselor thoroughly agreed with us. "Too many parents," he said, "are pressuring their children these days. If more parents had your courage and understanding . . ."
Eloise eloped at seventeen.	. . . a darling boy from a lovely family. Both he and Eloise are so mature for their years. There's such a difference in the maturation of children, don't you think?
Father lost his job.	We've always dreamed of John's taking a sabbatical. This year we just decided to take the bull by the horns. There are so many things he's always wanted to do. Maybe this year is the year to write The Book.

The Christmas Letter should finish on a note of restrained humility and well-bred religious feelings: "We are truly thankful that this Blessed Season

Continued on page 160.



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1. Schleif, R.H.: J.A.PH.A., 46:179,1957 *U.S. Pat. No. 3,062,714

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In transferring patients to low-dose Norinyl-1 from higher-dosage oral contraceptives, some breakthrough bleeding may occur in the early cycles. In the majority of cases the bleeding episode is mild and self-limited. The long-term advantages of the lower dosage form should be weighed against the inconvenience of possible breakthrough bleeding in the individual patient.

Prescribing Information

Contraindications: Patients with any symptoms or history of thrombophlebitis, pulmonary embolism, liver dysfunction or disease, carcinoma of breast or genital organs, or undiagnosed vaginal bleeding.

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Precautions: Pretreatment physical should include examination of the breasts and pelvic organs, as well as a Papanicolaou smear. If endocrine or liver function tests are abnormal during therapy, repeat tests are recommended after the drug has been withdrawn for two months. Following administration of drug, preexisting uterine fibromyomata may increase in size. Careful observation and caution are required for patients with symptoms or history of epilepsy, migraine, asthma, cardiac or renal dysfunction, cerebrovascular accident, psychic depression, and diabetes. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated. Possible long-term effects of the drug on pituitary, ovarian, adrenal, hepatic or uterine function must await further studies. The physician should be alert to the earliest manifestations of thrombophlebitis and pulmonary embolism. The drug should be used judiciously in those young patients in whom bone growth is not complete. The age of the patient constitutes no absolute limiting factor, although treatment with Norinyl-1 may mask symptoms of the climacteric. The pathologist should be advised of Norinyl-1 therapy when relevant specimens are submitted.

Side Effects: The following have been observed with varying incidence in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms, breakthrough bleeding, spotting, change in menstrual flow, amenorrhea, edema, chloasma or melasma, breast changes (tenderness, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately postpartum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals, mental depression. Although the following side effects have been reported in users of oral contraceptives, no cause and effect relationship has been established: anovulation posttreatment, premenstruallike syndrome, changes in libido, changes in appetite, cystitislike syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, and itching. The following occurrences have been observed in users of oral contraceptives (a cause and effect relationship has neither been established nor disproved): thrombophlebitis, pulmonary embolism, neuroocular lesions.

The following laboratory tests may be altered by the use of oral contraceptives: increased sulfobromophthalein and other hepatic function tests, coagulation tests (increase in prothrombin, factors VII, VIII, IX and X), thyroid function (increase in PBI and butanol extractable protein-bound iodine and decrease in T^3 values), metyrapone test, pregnanediol determination.

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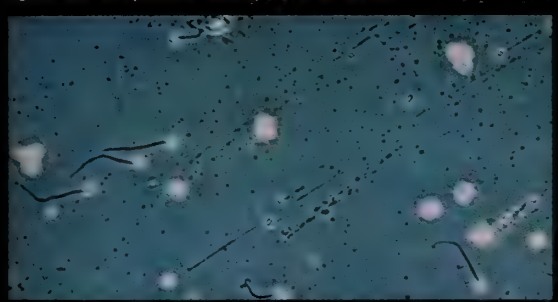
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The effectiveness of Norinyl-1 as a low-dose oral contraceptive may be explained by its possible multiple action. In addition to its primary action of suppression of ovulation, Norinyl-1 may offer additional protective mechanisms... (1) creation of a cervical mucus that may be hostile to sperm penetration, and (2) development of an endometrium that may be out of phase with nidation. These effects are illustrated below.

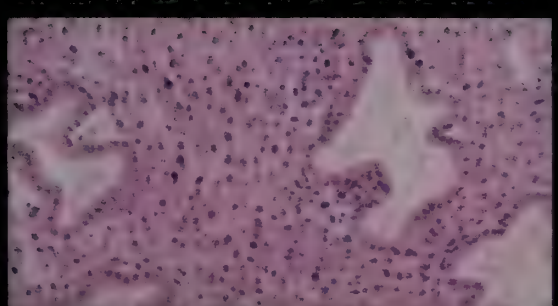
Untreated Patient



Cervical mucus at midcycle is usually thin and watery, with Spinnbarkeit (stretchability) of 15 to 20 cm.

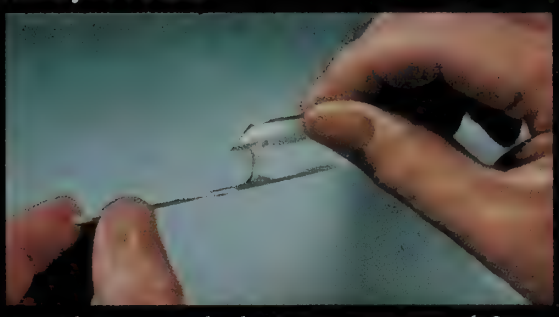


Spermatozoa appear healthy, active, freemoving.

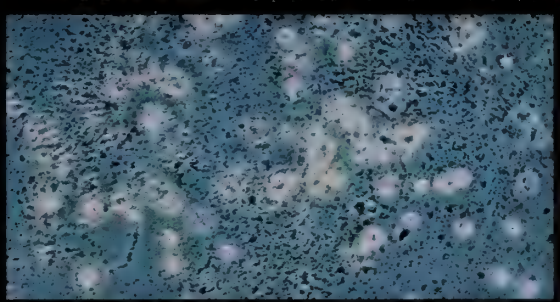


Endometrium of untreated patient is receptive to the fertilized ovum during secretory phase.

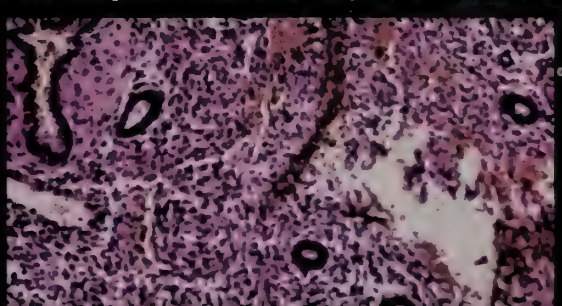
Norinyl-1 Patient



Cervical mucus at midcycle is scanty, viscous—with Spinnbarkeit of 1 cm. or less.



Immobile spermatozoa as they appear in cervical mucus taken from patient treated with Norinyl-1.



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Turn page for contraindications, precautions and side effects.

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Contraindications: Tuberculous, fungal, and most viral lesions of the skin (including herpes simplex, vaccinia, and varicella). Not for ophthalmic use. Contraindicated in individuals with a history of hypersensitivity to any of the components. *Precautions:* Synalar preparations are virtually nonsensitizing and nonirritating. However, the solution may produce burning or stinging when applied to denuded or fissured areas. In some patients with dry lesions, the solution may increase dryness, scaling or itching. Where severe local infection or systemic infection exists, the use of systemic antibiotics should be considered, based on susceptibility testing. While topical steroids have not been reported to have an adverse effect on pregnancy, the safety of their use on pregnant females has not absolutely been established. Therefore, they should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time. *Side Effects:* Side effects are uncommon with topical corticosteroids. As with all drugs, however, a few patients may react unfavorably to Synalar under certain conditions. In such cases the agent should be discontinued and appropriate measures taken. *Availability:* Synalar (fluocinolone acetonide) Cream 0.025%—5, 15 and 60 Gm. tubes and 425 Gm. jars. Cream 0.01%—15, 45 and 60 Gm. tubes and 120 Gm. jars. Solution 0.01%—20 and 60 cc. plastic squeeze bottles. Ointment 0.025%—15 and 60 Gm. tubes. Neo-Synalar® (neomycin sulfate 0.5% [0.35% neomycin base], fluocinolone acetonide 0.025%) Cream—5, 15 and 60 Gm. tubes.

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ANSWER: This seemingly annoying complication during a routine laboratory procedure actually represents a great help in the diagnosis of this case. Coagulation at 56 C. establishes the presence of a pyroglobulin in the patient's serum. Pyroglobulinemia is found most commonly in multiple myeloma but occasionally in other protein disorders such as macroglobulinemia.

H. H. Zinneman, M.D.
Minneapolis, Minnesota

Sleep Disturbance in An Infant

QUESTION: Twice recently, shortly after retiring, I've been awakened by a call from two frantic mothers saying their children, aged 10 and 13 months respectively, had awakened from a deep sleep crying out in terror. "Would you come right over?" I did, only to find the children in each instance sound asleep! What's the explanation and what can the busy physician do to avoid such unwelcome calls?

ANSWER: No one yet knows fully why this phenomenon occurs, but it is not unexpected in children in this age range. The most logical explanation is that the child is carrying over unresolved tensions of the day into the night and he may be dreaming—a possibility which all too often is overlooked.

To avoid being called unnecessarily the physician can do two things: (1) he can discuss the possibility of such an occurrence with the parent and prepare him for its happening; (2) if it happens he can ask the parent to determine if the child (a) has a temperature, (b) is cold, (c) is hungry, (d) is wet or soiled. Provided everything is in order, the child should be thoroughly awakened, given comfort and reassurance for a while, and then placed in his crib, perhaps with a favorite toy. In the majority of instances the child will shortly resume his sleep. Parents should be discouraged from taking their children into bed with them under such circumstances. Inevitably this creates other problems.

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The Viewing Box

Unusual Intra-Abdominal Calcification

This is a plain film of the abdomen obtained prior to exploratory laparotomy on a 30-year-old white male suspected of having intraperitoneal hemorrhage. He had suffered a deep stab wound in the left flank the evening of admission, but claimed to have been in excellent health all of his life prior to this episode. The abdominal films showed no visible free air or intraperitoneal fluid. At surgery a lacerated spleen was found and removed. The surgeon then correctly identified the obvious plain film finding of the right lower quadrant calcifications.

What is your diagnosis? (See next page.)



Figure

Diagnosis: Fecaliths in a Meckel's Diverticulum

A narrow-necked Meckel's diverticulum measuring 5 × 5 cm. was excised and found to contain five triangular-shaped stones which on subsequent section showed a soft fecal core. The diverticulum also contained a small focus of ectopic gastric mucosa and showed minimal chronic inflammatory changes.

In 1812 Meckel first described the entity as a true diverticulum, that is, one with a complete intestinal wall. The incidence of this diverticulum, which represents embryologic remnants of the yolk stalk and the omphalomesenteric attachment, is approximately 2% in autopsy and surgical material. It is seen three times as commonly in males as in females. The diverticulum is usually found one to three feet from the ileocecal valve on the antimesenteric side of the ileum, and most often is conical in shape with a wide mouth.

Many complications of a Meckel's diverticulum have been reported, such as peptic ulceration from heterotopic gastric mucosa, inflammation, intussusception, neoplasm, internal hernia, and volvulus. One of the rarest complications is coprolith formation. Even rarer is demonstration of the coprolith by x-ray.

Complications from the stones themselves have been reported, including hemorrhage, inflammation, and perforation with the stone lying free in the peritoneal cavity. Recently reported have been several cases of ileal obstruction distal to a diverticulum following passage of a stone that formed within it.

Diagnosis of this condition has been extremely rare, let alone the infrequent preoperative diagnosis of a diverticulum itself. With the use of barium studies and certain radiographic signs, Meckel's diverticulum might be diagnosed more often before the abdomen is opened. Certainly the finding of right lower quadrant calcifications, no matter what morphologic form they might have, should make one consider the possibility of stones within a Meckel's diverticulum. Lerner et al.[4] reported a calculus within a constant gas-filled pocket in the right lower quadrant. This should be highly suggestive of the diagnosis. When sought for, the diverticulum can often be outlined during the course of a barium meal study, occasionally showing an unexpected radiolucent stone as a negative filling defect. Bischoff and Stampfli[1] reported two cases of Meckel's stone in which the stones showed as a "ribbon-like" calcification which they thought might be characteristic.

To be included in the differential diagnosis of a right lower quadrant stone would be a coprolith in the vermiform appendix, or a stone in a low-lying gallbladder or a ptotic kidney.

Charles Nicolette, M.D.*
Minneapolis, Minnesota

*Fellow, Department of Radiology, University of Minnesota Hospital and Hennepin County General Hospital.

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Trauma Conference

Traumatic Rupture of the Testicle

BLUNT TRAUMA to the testicle resulting in rupture without an accompanying laceration of the scrotum has long been considered a rare event. Thirty-five cases have been reported in the literature to date.[3,18] This paper will discuss an additional case and will present a review of the literature.

Case Report

A 23-year-old active duty serviceman received a blow to his left testicle when he slipped and fell off a box. His initial pain was severe, and he was sent to a local hospital where he received conservative treatment consisting of scrotal elevation, ice packs to the scrotum, antibiotics, Chymoral and large doses of demerol with partial relief of symptoms.

Three days later he was transferred to the Minneapolis Veterans Administration Hospital. Initial examination revealed a swollen and painful left testicular mass which did not transilluminate along with ecchymotic areas on the penis and left side of the scrotum. The urine contained no red blood cells, and a number 16 Fr. Robinson catheter was easily passed through the entire length of the urethra. The remainder of the physical examination was normal except for a temperature of 100.2° F.

A preoperative diagnosis of either testicular rupture or torsion of the spermatic cord was made. Three days following admission, surgical exploration through a left scrotal incision was performed, revealing a 4.0 by 6.0-centimeter hematocele under tension (Figure 1). After the hematocele was evacuated, a 3.0-centimeter transverse laceration through the tunica albuginea with extrusion of testicular tissue was noted in the lower pole of the testis. The devitalized parenchymal tissue was debrided by sharp dissection. The tunica albuginea was then closed with interrupted 3-0 plain catgut sutures, and the scrotal incision was closed around a Penrose drain. The estimated reduction of testicular mass at surgery was 15 per cent. The postoperative course was uneventful.

A one-month follow-up examination revealed the left testicle to be of approximately normal size and non-tender, and the scrotal incision was well-healed.

Review of The Literature

The first reported case of traumatic rupture of the testis was by Cotton in 1906.[1] Since then additional cases have been reported.[2-10,13-18] McCormack[3] collected 27 cases and added five additional ones. No testicular disease was present in any of these cases prior to injury except in one case where a seminoma* was found to antedate the trauma.[8] No cases of ectopic testicular

*See Test Your Word Score Page 53.

rupture have been reported. More than half of the reported cases have occurred during participation in athletic events. Wesson[9] reported his experience with a case of traumatic rupture of a solitary testicle.

Most of the cases have occurred in patients less than 30 years of age with an age range of eight to 49 years. All patients have been younger than 50 years, substantiating McCrea's statement regarding the frequency of this injury being confined to the period of increased physical activity.[6]

It is the authors' personal conviction that this entity, along with undiagnosed torsion of the spermatic cord, may be far more frequent than has been reported, as evidenced by the large number of atrophic testicles found during routine physical examination. A more aggressive surgical approach, as recently recommended by a number of urologic surgeons, may show this to be the case.

Etiology

Contusions of the testicle are not an uncommon occurrence, but because of its shape and mobility in the scrotal sac and its tough inelastic capsule (tunica albuginea), a laceration of the testis is very rare. According to Wesson,[9] approximately 110 pounds of force is necessary to rupture the testis when the latter is caught between two unyielding objects. McCrea[6] feels that the blow must be delivered with a sudden compressing or crushing force and must be directed straight or obliquely upward in order to impinge the testicle between the pubic bone or thigh and the hard traumatizing object.

McCormack,[3] in two of his cases, questioned whether a missile traveling at moderate velocities might have caused the testicle hanging loose in the scrotum to literally explode on contact, although he did not rule out that the testis in these cases might have been forced against the pubis, permitting a crushing blow.

Pathology

The gross pathology of traumatic rupture of the testis includes:

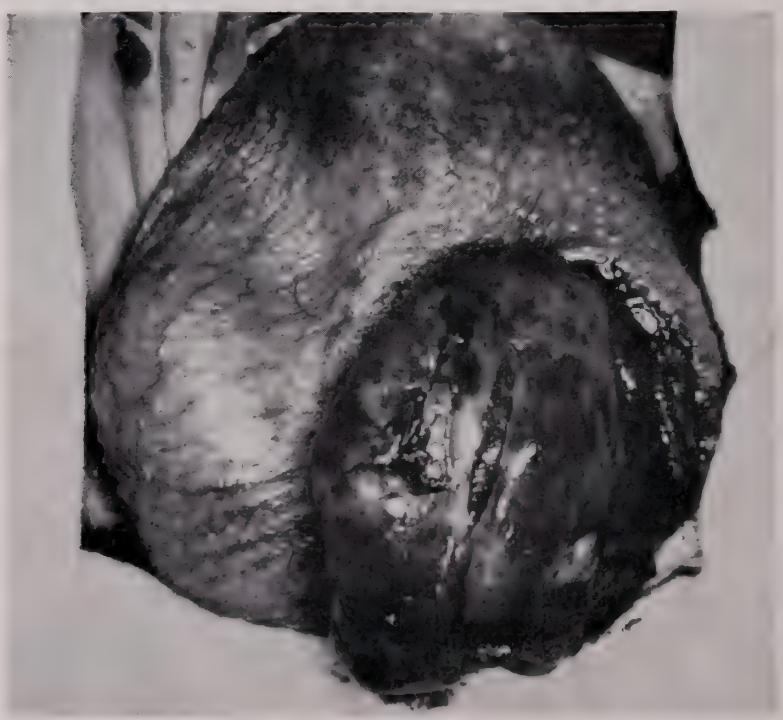


Fig. 1—Four-by-six centimeter hematocele surrounding the left testicle.

1. Ecchymosis and edema of the scrotum and contiguous areas.
2. Rupture of the visceral layer of the tunica vaginalis.
3. Hematocele with fresh blood or blood clots between the visceral and parietal layers of the tunica vaginalis.
4. Rupture of the tunica albuginea with resultant extrusion of testicular tissue which is usually devitalized. The tear is generally transverse; however, a longitudinal tear was reported by Dundon.[10]
5. Associated injuries of the epididymis, spermatic cord, penis, urethra or other testicle.

Signs, Symptoms and Diagnosis

The signs and symptoms following traumatic rupture of the testis are not distinct from those following other types of trauma, or from torsion of the spermatic cord, testicular tumors or inflammatory diseases such as epididymo-orchitis. In cases of traumatic rupture there may be pain, swelling, obliteration of the scrotal skin folds, ecchymosis, skin abrasions, nausea, vomiting, shock and fever.

Pain is usually present to some degree following the injury. It may be minimal to severe and may last from minutes to weeks. The scrotal swelling with resultant loss of skin folds is usually gradual. It seldom becomes excessive unless associated with further scrotal injury such as rupture of the spermatic cord. Occasionally when a patient is seen days or weeks following the injury, only a moderately enlarged epididymo-testicular mass is found, and a diagnosis of chronic epididymo-orchitis is mistakenly made. Ecchymosis along with abrasions of the scrotal skin is seen in most cases following the acute injury. These ecchymotic areas may extend onto the thighs, penis and perineum. Nausea, vomiting and shock have been reported following traumatic rupture of the testis; however, these have not been outstanding characteristics. Several patients with fevers ranging from 99° to 104° F. have been reported.[2-3]

The complications following traumatic rupture of the testicle are secondary infections, abscess formation and atrophy.[12] McCormack[3] has suggested the possibility of an auto-immune reaction to the patient's own extravasated sperm. Whether or not spermatozoa from extravasated testicular tissue actually act as antigens and cause the production of antibodies is not known.

Treatment

Treatment should be instituted as soon as possible when traumatic hematocele is suspected or diagnosed by needle aspiration of blood. Surgical exploration with evacuation of the hematocele and inspection of the testis, epididymis and spermatic cord should be undertaken promptly. If rupture of the testicle is found, the devitalized testicular tissue should be debrided and the defect in the tunica albuginea closed with interrupted horizontal mattress sutures of 3-0 plain catgut. The scrotal cavity is drained with a Penrose drain. Testicular rupture with total extrusion of testicular tissue may have to be treated by total orchiectomy. If, however, the tunica albuginea is not severely damaged or infarcted, the capsule might best be left in place, as in subcapsular orchiectomy, since the capsule has been shown to contain Leydig-like cells which are hormonally functional.[12]

Summary

Traumatic rupture of the testicle is rare. Only 36 cases including our own

have been reported in the literature. We feel that many cases of testicular atrophy found during routine physical examination are due to undiagnosed traumatic rupture of the testis or undiagnosed cases of spermatic cord torsion. We are also of the opinion that all cases of traumatic hematocele should be explored as soon as possible after the injury with the hope of salvaging more functional testicular tissue.

John J. Wedge, M.D.*
Clyde E. Blackard, M.D.*
Minneapolis, Minnesota

*Department of Surgery (Urology), Veterans Administration Hospital and University of Minnesota Hospitals.

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Avicenna* Cures a Melancholic

A certain prince was afflicted with melancholia and suffered from the delusion that he was a cow. Every day he would low like a cow, causing annoyance to everyone, and crying, "Kill me, so that a good stew may be prepared from my flesh"; until matters reached such a pass that he would eat nothing, while the physicians were unable to do him any good. Finally Avicenna, who was at this time acting as prime minister to 'Ala'u'd-Dawla ibn Kakuya, was persuaded to take the case in hand. First of all he sent a message to the patient bidding him to be of good cheer because the butcher was coming to slaughter him, whereat the sick man rejoiced. Some time afterwards Avicenna, holding a knife in his hand, entered the sick room, saying, "Where is this cow, that I may kill it?" The patient lowed like a cow to indicate where he was. By Avicenna's orders he was laid on the ground bound hand and foot. Avicenna then felt him all over and said, "He is too lean, and not ready to be killed; he must be fattened." Then they offered him suitable food, of which he now partook eagerly, and gradually he gained strength, got rid of his delusion, and was completely cured.**

*See Test Your Word Score Page 53.
**Edward Browne: Arabian Medicine.

Sources of sinus headache



REGION OF SENSATION

FRONTAL SINUS—headache localized over the frontal region, commonly beginning in the morning. Eyes painful to touch, may be slight swelling over eyes, puffy eyelids.

SPHENOID SINUS—most difficult to diagnose. Headache or sense of pressure over vertex. May be pain in ear or mastoid region.



MAXILLARY SINUS—headache and tenderness under eyes at top of cheekbones, usually starting in early afternoon. Possible swelling of cheek. Pain in jaw and back teeth.

ETHMOID SINUS—headache, tightness in upper part of bridge of nose and well down its sides. Pain, deep-seated behind the eyes and in inner corners of the eyes.



TURBINATES—pain along medial and lateral walls of the inside of the nose. Headache in frontal region, along supraorbital ridge, a feeling of fullness in the head.

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Tumor Conference

Brotherly Lumps

Familial Occurrence of Chemodectoma

CAROTID BODY tumors are rare. Since Von Haller first described the carotid body in 1743, slightly over 500 tumors of that body have been reported. One of the side effects of their treatment is that it usually induces an uncontrollable desire to write in the surgeons who remove these tumors. It is possible we could have resisted had this not been a well confirmed familial occurrence.

Case Report

A 43-year-old white male sheetmetal worker was admitted to the Neurology Service of the Minneapolis Veterans Administration Hospital because of increasing difficulties in performing routine work. He complained of bifrontal headaches and difficulty remembering measurements in sheetmetal lay-outs.

The past history revealed the following positive findings: (1) Appendectomy in 1942, (2) Pilonidal cystectomy in 1949, (3) A left neck mass first noted while in the Navy in 1958 and slowly increasing in size, (4) Herniated nucleus polyposis in 1961, (5) Unroofing of a perirectal abscess in 1961.

Physical Findings

The patient was a well-muscled white male with mild bilateral exotropia with ptosis of the left eyelid and anisocoria,* the left pupil being smaller than the right. There was a 5 x 4 x 4 cm. mass in the left neck that transmitted a carotid pulse. The mass was prominent and easily palpable bimanually in the pharynx. The rest of his physical examination was within normal limits.

Laboratory Findings

Complete blood count and urinalysis were normal and the VDRL was negative. The 24-hour RAI 11%, alkaline phosphatase 11.2, serum creatinine 1.2, protein-bound iodine 8.3, calcium 9.7 mgm.%., phosphorous 3.8 mgm.%., CO_2 combining power 26.5 mgm.%., chlorides 105 mgm.%., sodium 142 mgm.% and potassium 4.6 mgm.%.

Chest x-ray, skull x-rays, brain scan and electroencephalogram were all normal. The thyroid scan was normal without any uptake over the left lateral neck mass.

A left carotid angiogram clearly demonstrated the extremely vascular mass in the left neck at the level of C2-C3 (Figure 1). A compression angiogram revealed excellent filling of the right cerebral vessels from the left, showing good circulation cross-over.

Operation

On the basis of the physical findings and the angiographic picture the patient had an exploration of the left neck. The carotid vessels were isolated above and below the carotid body tumor (Figure 2). Precautionary preparation for an intravascular shunt

*See Test Your Word Score Page 53.

was made but not required in the dissection. This tumor was excised by subadventitial dissection. The internal carotid artery was narrowed where compressed between tumor and the mastoid process. When undistended with blood the chemodectoma measured 3.5 x 2.5 x 2 cm. The histologic picture is shown in Figure 3. Postoperatively, the patient did well except for pain in the upper portion of the incision. He is being evaluated for possible hyperthyroidism.

The patient's brother, who is five years older, had been operated for a right-sided neck mass two months previously in Detroit. This was also a carotid body tumor.

Comment

This rare tumor represents a non-chromaffin paraganglioma of the carotid body. The normal carotid body measures about 6 x 4 x 2 mm. and is located medially and behind the carotid bifurcation. The blood supply is chiefly from the external carotid and possibly a branch from the thyrocervical trunk. The carotid body has no endocrine function, although an occasional tumor of the body may secrete epinephrine.[1] De Costra in 1926 was the first to suggest that the carotid body might be a chemoreceptor. Chemoreceptor bodies are located at the carotid bifurcation, jugular bulb, aortic arch, and on the auricular branch of the vagus nerve, tympanic branch of the glossopharyngeal nerve, inferior ganglion of the vagus nerve and bifurcation of the aorta.[1] Tumors in these other sites are even more rarely seen.

The usual carotid body tumors are ovoid, firm, encapsulated, trabeculated and vascular. Histologically, carotid body tumors consist of large, eosinophilic cuboid or polyhedral* cells arranged in alveolar pattern, separated by thick, vascular trabecula[1] (Figure 3).

Familial Incidence

Chase noted the familial incidence of carotid body tumors as early as 1933.[2] Familial incidences of chemodectomas have since been reported by several writers.[3-5] *Bilateral* carotid body tumors are more likely to occur on a familial basis than in a sporadically occurring carotid body tumor.[4,6]

Carotid body tumors do have a malignant potential that has been reported

*See Test Your Word Score Page 53.

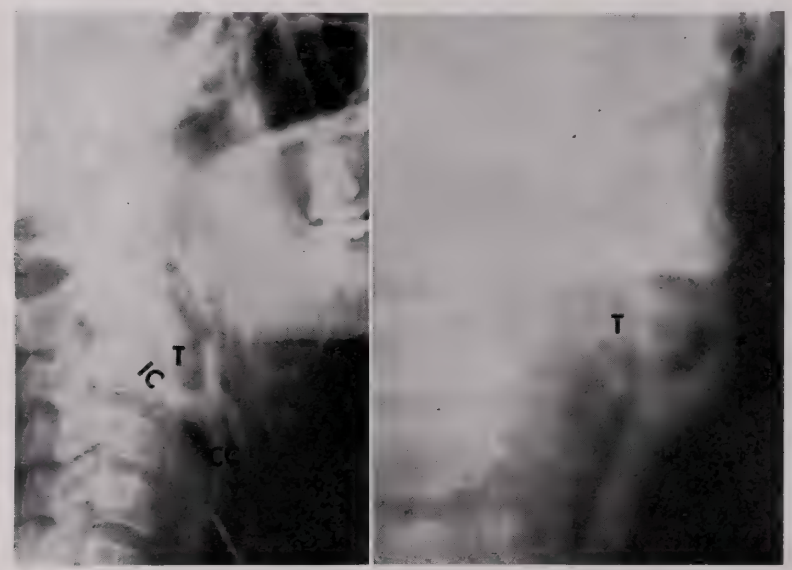


Fig. 1—(left) A lateral carotid angiogram showing the contrast material in the very vascular carotid body tumor. (right) An A-P angiogram showing the location of the carotid body tumor deep to the vessels. The internal carotid artery is displaced far laterally.

as 6.4% to 10%. Local and distant metastases have been reported.[6,7]

Differential Diagnosis

On a statistical basis, metastatic squamous cell carcinoma, brachial cleft cyst, metastatic cancer from the thyroid, lymphadenopathy, neurofibroma and metastasis from a distant site are all more likely diagnoses for a mass in the

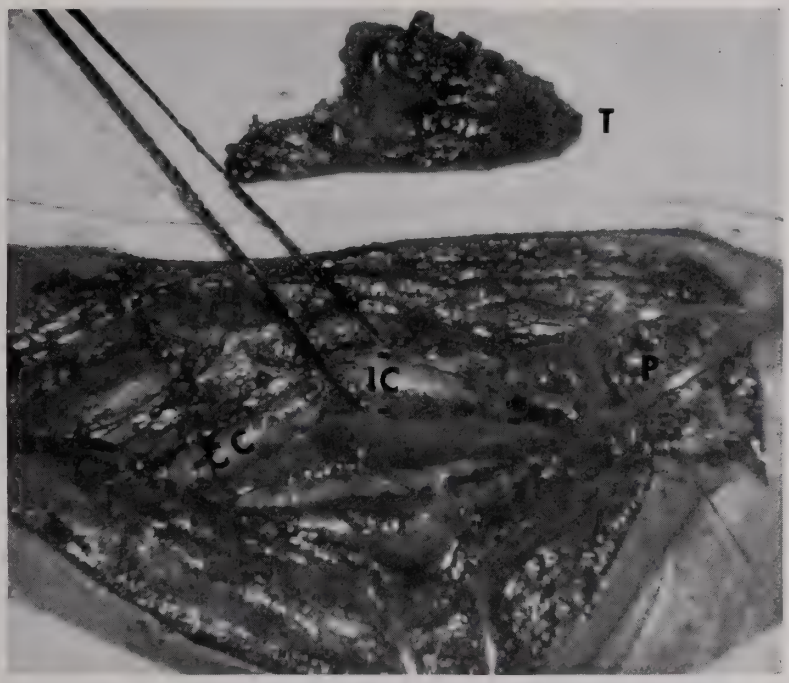


Fig. 2—A view at the time of operation. The markers show the narrowing of the internal carotid (IC) just under the parotid gland (P). The external carotid is behind the internal carotid. The tumor (T) is on the towel above.

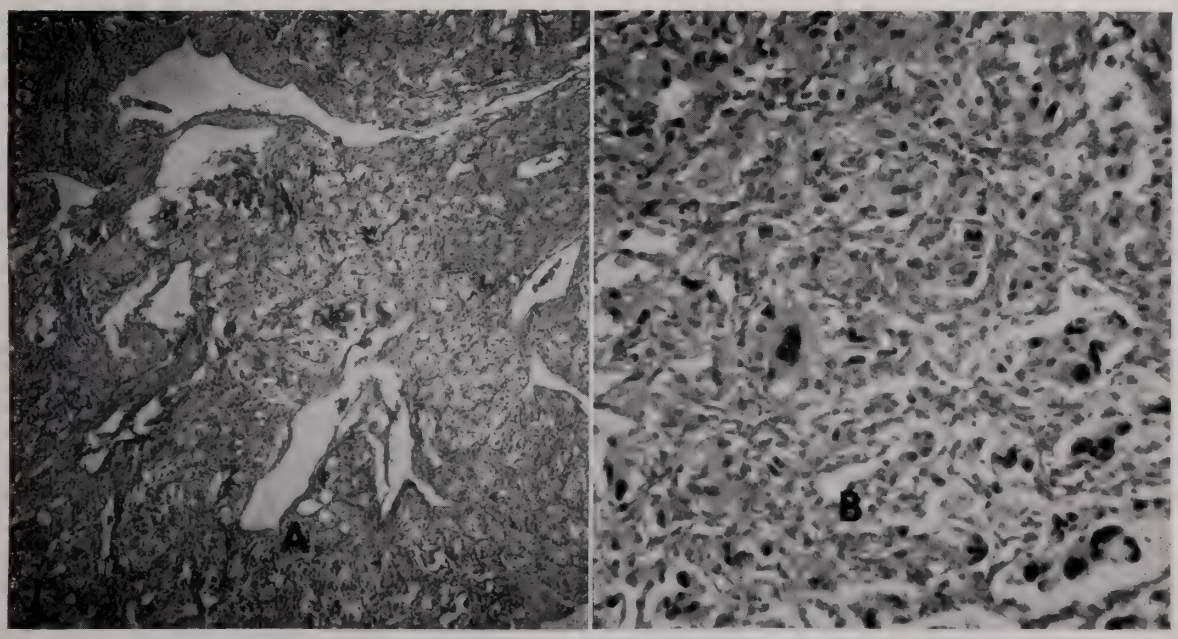


Fig. 3—(A-left) A low power view of the carotid body tumor showing the typical pattern and the numerous vascular spaces in the tumor. (B-right) A higher powered view of the tumor.

lateral neck.[8] The usual physical findings of a mass located just below the angle of the mandible that is non-tender and of long duration, that can be moved in the horizontal but not the vertical position, is characteristic but not diagnostic of a chemodectoma. Tumor involvement has been observed to induce a facial or accessory nerve weakness or, infrequently, a paralysis of the tongue or a Horner's syndrome. An occasional patient may have fainting with a carotid sinus syndrome.[9] Carotid body tumors extending deep to the carotid system can cause dysphagia.

Carotid angiography demonstrating the characteristic vascular tumor stain is the most reliable tool in the diagnosis of carotid body tumors. The angiogram may show an increase in the angle of the carotid bifurcation on the involved side and give helpful information on the cross-over of the cerebral circulation.

Risk of Operation

Any appreciation of the high-flow vascularity of these friable tumors would make it apparent that a casual incision biopsy would be a startling affair. In light of this vascularity and the position surrounding the carotid bifurcation, it is not surprising that Riegner's first attempt to excise a carotid body tumor in 1880 resulted in the patient's death. Mydl in 1886 resected a carotid body tumor. This patient survived—but with hemiplegia and aphasia. Albert in 1889 performed the first successful excision of a carotid body tumor without sacrificing the carotid vessels.

The fact that carotid body tumors do not regress but continue to grow, albeit slowly, has led surgeons to continue to attempt their removal. Radiation is of limited, if any, value.[6,7]

In earlier years when ligation of the carotid system was frequently performed, the operative mortality ranged from 20% to 58%—with more frequent brain damage. It is understandable then that up to a decade ago it was felt by many that attempts at removing carotid body tumors were not justified.[9] Two things have reduced surgical mortality to acceptable levels as low as 1.5% in Rushes' review:[10] wider familiarity with vascular surgical techniques, such as the internal vascular shunt, and diagnostic angiography.

As a final note to this case, it is difficult to know whether the narrowing of the internal carotid by the tumor contributed to the patient's neuropsychiatric problems. There has been no dramatic change to date.

Martin Beard, M.D.*
Donald G. McQuarrie, M.D.*
Minneapolis, Minnesota

*Department of Surgery, Veterans Administration Hospital and University of Minnesota, Minneapolis, Minnesota.

Acknowledgment

We are very grateful to Dr. Szilagyi of Detroit, Michigan, for the report concerning the chemodectoma removed from the brother of the patient whose case is reported in this article.

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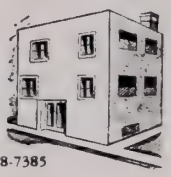
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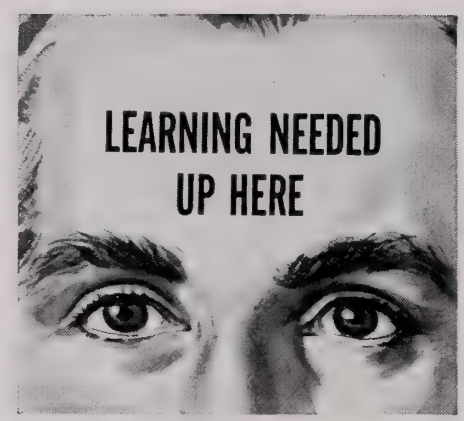


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Neurological Conference

Stroke Convalescence*

This case represents one of the more perplexing problems that can be encountered in medical practice. The patient to be discussed has been partially disabled by a stroke in a way which is overtly inapparent to most people, and yet extremely obvious to him. Previously the patient had been a very good painter, but now he has lost the skill which had taken years of experience to develop. As the history and discussion are presented, the manifold ways in which this illness has affected both him and his family will become apparent. At this time, his future depends greatly on what we have to offer him.

History of Present Illness

Dr. Paul Martin:**

This 48-year-old painter first visited the University of Minnesota Medical Center on November 3, 1965. He was referred by his private physician for therapy to improve the function of his left arm. Prior to the present illness he had always enjoyed excellent health. On August 11, 1964, the patient had awakened and prepared to go to work; however, as he climbed into his truck, he noticed that he had difficulty raising his left arm to put the key into the ignition. Not thinking much of this at that time, he drove on to work. When he arrived at work, he found that he couldn't open the door of the truck to get out.

He was taken to his local hospital where he presented with a left hemiparesis involving primarily his left face and arm. An angiogram was performed which revealed a complete occlusion of the right internal carotid artery. Subsequently he was treated conservatively and much of the obvious paresis gradually cleared. The patient became increasingly aware of the fact that coordination in his left hand failed to improve. As a result, he found that he was unable to paint as he had before. After convalescing at home for about two weeks, he was seen by a neurosurgical consultant who recommended that an endarterectomy be performed. This was attempted, but the patency of the right internal carotid system was not re-established.

The patient returned to work for one month. Finding that he could not do the quality of work he had previously done, he became disgusted, quit his job and stayed home. Since then he has been extremely depressed and has resorted to drinking, which, according to him, made him feel "more normal." He had previously been quite successful as a painter, earning approximately $4.00 per hour as a foreman. Now his alcoholic intake is about one pint a day. Most of the time he sits at home doing nothing but brooding about his inadequacies. Prior to his present illness, he never had more than one to two shots in an evening.

While being questioned about his past history, the patient stated that he remembered two occasions during the previous three years when he had reached for an object with his left hand and missed. No other neurological symptoms were evident in the past history. He has had an elevated blood pressure occasionally in the past which was treated medically. During his initial hospitalization, a glucose tolerance test was suggestive of diabetes and he was placed on a diabetic diet.

*Neurological Conference held December 2, 1965. These conferences are an integral part of the comprehensive Clinic Program at the Universiiy of Minnesota Hospitals.

**Student Doctor, University of Minnesota Hospitals.

Physical Examination

On physical examination, the patient was a very well-appearing man with an outgoing, friendly personality. His blood pressure was 170/110 mm.Hg. bilaterally. Positive findings were confined to the lungs and nervous system. Regarding the former, a slight decrease in vital capacity was suggestive of early emphysematous changes. Neurological examination showed a mild persisting deficit in the left central seventh function and a slight incoordination of the left upper extremity. Dysmetria in the left arm and hand was apparent when he attempted volitional maneuvers. Questionable evidence of a peripheral neuropathy was found on sensory examination. Tests of reflex activity and motor strength showed no abnormalities. The visual fields were normal. A well healed surgical scar was present over the right anterior neck.

Routine laboratory data included a normal hemogram, urinalysis, and serology. The blood urea nitrogen was within normal limits. A glucose tolerance curve was again suggestive of mild diabetes, rising to 237 mg% at one hour and returning to 100 mg% at two hours. A chest x-ray was normal. Significantly, an electrocardiogram revealed evidence of a possible old posterior myocardial infarction, although this could not be documented historically.

Dr. Robert W. Soll:*

Surgical endarterectomy in the presence of a complete occlusion of the internal carotid artery must be done within the first six to eight hours after the occlusion occurs if it is to be successful. This is probably due to the formation of a thrombus distal to the occlusion extending through the carotid siphon in the base of the skull. The removal of such a thrombus is virtually impossible. On the other hand, if the thrombus is removed in the presence of a completed stroke, there is great danger of hemorrhage into the infarcted brain. An insufficiency resulting from a narrowing of the vascular lumen, on the other hand, is very amenable to surgery. Since this patient did have a complete occlusion of the right internal carotid artery and a prolonged interval had occurred between the onset of his symptoms and the attempted surgery, the likelihood for successful removal of the obstruction was virtually nonexistent.

Psychological Evaluation

Dr. John Brantner:**

Both the patient and his wife were interviewed. A thorough battery of brain function tests were administered to check for signs of brain damage. His I.Q. as measured by the full scale Wechsler Adult Intelligence test was 96, an average score which correlated well with his vocational achievement. On the other hand, the sub-test patterns were highly suggestive of brain damage. Both immediate and remote memory were reduced significantly. He was incapable of solving the Porteus Mazes, contrary to what would be expected on the basis of his intelligence. The most gross distortions appeared in his attempts to copy geometric figures since these involved hand-eye coordination. He was totally incapable of drawing a pencil line which would pass between two points 3/8 of an inch apart. Ballistic distortions appeared when he attempted to copy geometric figures; in other words, incoordination was quite gross and very evident. On the basis of this, it could be assumed that he would be completely incapable of painting in situations where one color met another. Although he was using his dominant hand, the left hand, his performance with that hand was quite similar to the performance usually seen with a nondominant hand.

Doctor Martin:

These findings correlate well with the patient's complaint of inability to "finish the wall." This is an expression used by painters for painting to the

*Neurologist, University of Minnesota Hospitals.
**Associate Professor, Clinical Psychology, University of Minnesota Hospitals.

line where the wall meets the ceiling.

Depression Following Stroke

Dr. Brantner:

The Minnesota Multiphasic Personality Inventory reflected a mild to moderate reactive depression in a passive somewhat dependent man. Many of these test results were ambiguous in view of his drinking, because similar findings such as incoordination can be obtained in persons following a period of intoxication. The patient's wife had mentioned that she disliked her husband's drinking although she understood why he did it and hoped someone would be able to do something about it. Other than housework, which he doesn't like, there is nothing for him to do. Apparently he has rarely been sober for a period of more than a few days during the past year. His drinking usually has been limited only to the point at which he staggers, never to coma.

The wife's multiphasic was entirely within normal limits. She appeared to be a mildly overcontrolled person and perhaps under very mild tension.

It would be interesting to maintain the patient in a controlled environment where he was not permitted any alcohol intake for a period of about 10 days, and then repeat the testing.

Physical Medicine Evaluation

Dr. Frank Meelhuysen:*

There was no decrease of strength in the patient's left extremities compared to his right. The range of motion in his left arm and leg was within normal limits except for diminished supination of the forearm. A persisting mild spasticity was still evident in the left biceps and forearm pronators. Mild proprioceptive loss was suggestive on the left side. These three factors produce most of the problems he has with coordination. It was felt, however, that these disturbances were not severe enough to require intensive therapy. Apparently the patient's private physician has suggested that the patient use his right hand more; however, I feel that increased use of his left hand also will gradually enable him to develop more skill, considering the mild degree of disability which seems to be present.

Location of Cerebral Lesion

Dr. Richard Magraw:**

Where is the probable location of the patient's lesion?

Dr. Soll:

The entire lesion may be diffuse, but most of the damage is probably located in the region of the genu and anterior portion of the posterior limb of the right internal capsule. The incoordination could be either on the basis of the spasticity or by virtue of the involvement of corticofugal fibers passing through this area and extending from the frontal lobe to the cerebellum via the pontine nuclei which bring the cerebellum under the control of psychosensory association areas of the cortex.

Doctor Martin:

The neurological findings were so minimal that he performed perfectly on finger to nose, but tended to error on reaching for a remote point in space. This mild disturbance as pointed out by Dr. Meelhuysen might be manifested

*Assistant Professor, Physical Medicine and Rehabilitation, University of Minnesota Hospitals.
**Director, Comprehensive Clinic Program, University of Minnesota Hospitals.

functionally by the fact that he tends to "streak" when painting.

Dr. Soll:

Such a loss, although minimal, can be as important to the patient as the loss of function of a finger would be to a pianist.

Dr. Magraw:

Why wasn't the patient attempting to improve himself if repeated use of his left hand would do this?

Dr. Meelhuysen:

I feel that the degree of cerebral damage directly correlates with the rehabilitation potential of a patient. Both physical as well as mental factors affect a patient's ability to recover from a disability, and certainly both are significantly involved in this case.

Social History

Mrs. Diane Crespin:*

I obtained the patient's permission to contact his former employer to learn more about his former job skills. The employer confirmed the fact that the patient had been a good worker and very dependable. He had been with them many years as a regular rather than seasonal worker. His salary was about $4.30 an hour or $170 a week as foreman of a painting crew. Following his convalescence, he failed to come to work on several occasions because of his drinking; however, prior to his present illness, drinking had never been a problem. The reasons given for his leaving the job was that the quality of his work was poor and it had to be done over again.

The patient now occupies his time by taking care of the housework and the dog. His current social security benefit is $124 a month. Since October, 1964, his wife has been working and she earns about $200 a month. Unfortunately they had accumulated no savings up to the time of his present illness.

Regarding the patient's reaction to his illness, he stated that he was having a difficult time adjusting to being unemployed. Also he found it hard to follow a diabetic diet since he was sitting home alone all day and eating. He would like to return to some type of work and had been trying to get employment as a taxi driver. He has shown some initiative in that he stated that he had been reading the want ads. Previously he had worked as a guitar player in restaurants and as a truck driver.

Other members of his family have all been in good health except one brother who died of a heart attack at age 48, a fact which has concerned the patient considerably. I feel that he would benefit by vocational rehabilitation. The best way to cope with his depression may be to find some way to return him to work. The former employer had thought the patient might like a job in a paint store, although this possibility has not been discussed with him.

Discussion

Dr. Meelhuysen:

Both the physical and psychological handicaps of the patient would tend to prevent his returning to his former job. Vocational counseling might be of benefit. This evaluation could be accomplished in the shop. I do not like the patient's idea of being a taxi driver, because of his reduced reaction time in case of an emergency as well as the responsibility involved in such

*Department of Social Service, University of Minnesota Hospitals.

a job. There are many other areas in which he might find a useful occupation. Painting might still represent the best type of work, not only on the basis of his past experience, but because it could be therapeutic by giving him a chance to use his left arm more. We should not expect the same quality of work that he has done in the past; for this reason, his supervisors should be informed of his present capability and the patient should be willing to take a lower position.

Dr. Magraw:

He has already tried painting and failed. It is possible that he has not yet recovered from the shock of this illness; consequently, simply returning to work may again leave him frustrated and more depressed. In addition to the patient's referral to rehabilitation, someone should work with him specifically in an attempt to stop his denial and face his loss. This would not have to be a formal psychiatric consultation; rather any one of his doctors could relate to him in this way.

Dr. Brantner:

This may be done during his contacts with skilled vocational counseling. The need for complete reorientation and vocational readjustment can be brought out. Factors which may help his reorientation are the occasional enthusiasm and eagerness which he has shown since his stroke. But he would have to be protected against failure which, if it occurred, would plunge him more deeply into depression.

Dr. Meelhuysen:

Special arrangements can be made with an employer which would enable the patient to work temporarily in a training capacity without pay. Similar arrangements have been made for many patients in the past. Prior to this the patient can spend one week, eight hours a day, in the pre-vocational shop to evaluate all of his present potential. Subsequently, admission to the hospital can be considered in order to obtain psychological testing in a more controlled environment.

Dr. Soll:

Short-term treatment of patients does not necessarily solve all of the problems an illness may present. This was true in this patient's case. A positive follow-through is a vital function for the physician in helping the patient return to a more normal life.

The plan for this patient was then summarized as follows:

1. Evaluation in the prevocational shop on an outpatient basis.
2. Appropriate vocational counseling and support with particular emphasis on protection against failure.
3. Reassurance by all therapists on the use of his left hand.
4. Psychological re-evaluation after the patient has been in a controlled environment one to two weeks in order to determine more definitely the degree of brain damage present.
5. Re-emphasizing to the patient the need for maintaining his diabetic diet.
6. Consideration of psychiatric consultation if the above plan fails to correct the patient's depression.

Robert W. Soll, M.D.
Chairman,
Community Services.

In youth we run into difficulties, in old age difficulties run into us.
—Josh Billings

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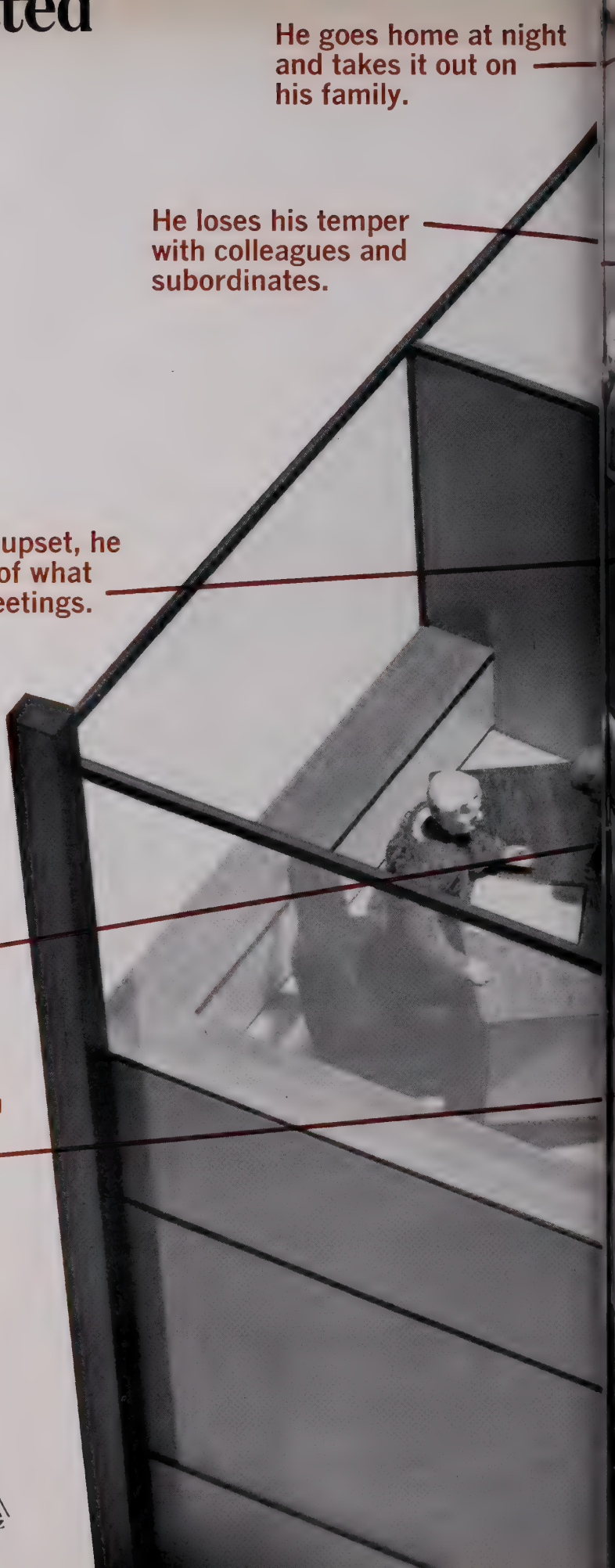
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Clinical Path Conference

Cyanosis, Seizures, and Hypernatremia in a Two-Week-Old Infant

Dr. W. Robert Anderson:*

A two-week-old infant was admitted to Hennepin County General Hospital for the second time because of "aspirating and a blue-gray color."

The child was born at Hennepin County General Hospital after a forty-week gestation complicated by slight first trimester spotting which lasted two weeks, and by rupture of the amniotic sac thirty-six hours prior to the delivery. The first stage of labor lasted five hours; the second stage was also rapid, being only five minutes in duration. No forceps were used. The third stage of labor lasted five minutes, and a circumvallate placenta with three cord vessels was delivered.

Postnatally the child did very well. He was noted to be minimally jaundiced on the third day of life. On the fourth day he was markedly jaundiced, and a bilirubin at this time was 24.5 mgm.%. An exchange transfusion was performed, which the child tolerated very well. There was no evidence of blood grouping incompatability and no sign of sepsis. The child remained vigorous throughout his hospital stay and was discharged on the tenth day, having received only the single exchange. On discharge he was given a complimentary pack of formula, containing six small bottles of ready-to-serve infant formula, and one can of concentrated infant formula, which required that it be diluted one to one with water before being given to the child. His discharge weight was 3390 grams.

During the first day after his discharge, he was fed the contents of the six small bottles, and then the contents of the can of concentrated formula without the necessary dilution. He was taking two ounces of this formula every two hours, and the mother noted that the child's diapers were consistently dry. He became increasingly fussy and irritable, and his respirations rapid. He then became cyanotic and was brought to the Emergency Room at Hennepin County General Hospital.

When first seen in the Emergency Room, he was acutely ill, cyanotic and in obvious shock. The respiratory rate was from 80 to 100 per minute, the heart rate was 60, the blood pressure was unobtainable, peripheral circulation was extremely poor, and the child was noted to be somewhat rigid. His temperature was 102° rectally and his weight 2,970 grams. The nares were clear, the mucous membranes of the mouth were dry and clear, the neck was supple and no masses were palpable. The lungs were clear to auscultation and the heart revealed no abnormalities. Peripheral pulses were unobtainable. Neurological examination revealed a severely distressed, agitated child whose movements were jerky and purposeless. No pathological reflexes were elicited.

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*Associate Pathologist, Department of Pathology, Hennepin County General Hospital.

His admission laboratory results revealed him to have a hemoglobin of 14 Gm.%, a white blood count of 14,200, a sodium of 163, a chloride of 144 and a potassium of 3.3 meq/L. A saphenous cut-down was done. The child was flushed initially with .2% saline, following which the heart rate improved to 140 to 160 beats per minute, although the respirations remained rapid. The child voided, and then was begun on 1/3 normal saline at the rate of 3,000 cc. /m^2/day, which was calculated to replace his deficits and keep up with maintenance fluids over the next 36 to 48 hours. Six hours after admission the sodium was 159, chloride 144, and potassium 3.3 meq/L. As his color improved from cyanotic to pink, his tone went from slightly rigid to opisthotonic. He was also noted to be exhibiting jerky, tremulous movements of all extremities and a high-pitched, unusual, somewhat strangulated cry. He was then sedated with .66 cc. of paraldehyde rectally and was started on phenobarbital, 5 mg./kgm/day. Seventeen hours after admission the sodium was 173, potassium 6.5, chloride 143 and CO_2 9 meq/L. Calcium at this time was 10.8, BUN 108, and blood sugar 145 mg.%. Thirty hours after admission the child's urine output remained good; sodium was 145, potassium was 6.4, chloride 141, and CO_2 13 meq/L. He was continued on half normal saline. Thirty-nine hours after his admission the sodium was 153, potassium 5.7, chloride 132, CO_2 13, and BUN 84. The last serum electrolytes obtained just prior to cardio-respiratory arrest on the second day after admission were: sodium 147, potassium 3.5, chloride 125, and CO_2 11 meq/L. The calcium at this time was 9.5 mg.% and the BUN 46. Blood and spinal fluid cultures obtained on admission were sterile. Following the assumption of the opisthotonic position and the beginning of the tremors of the extremities which were interpreted as definite seizure activity, he remained in approximately the same status until approximately fifty hours after admission, when he suffered cardio-respiratory arrest.

Discussion

Paul G. Quie, M.D.:*

This two-week-old male infant was hospitalized for the second time at Hennepin County General Hospital for aspiration and cyanosis. He was born here after 40 weeks gestation. The mother was multiparous and the first trimester of pregnancy was complicated by spotting. This frequently occurs, but the significance is not known. However, it is worth while reporting, since this may be important in the evaluation of the spectrum of maternal viral infections that may occur: for example, rubella or cytomegalic virus disease. The amnionic sac ruptured 36 hours prior to delivery and this obviously may predispose to neonatal sepsis. In most series, it is recognized that there is a high incidence of sepsis in newborns when membranes have been ruptured for greater than 24 hours. However, it should also be emphasized that upwards of 70 to 80% of infants in such instances are perfectly normal. Consequently, each situation must be considered individually. The delivery was rapid but apparently not precipitous; however, the possibility of a traumatic delivery must be considered. There is no evidence that central nervous system damage was present at birth. The placenta and umbilical cord were normal and afforded no clue to the problem involved. The infant was normal at delivery.

He was minimally jaundiced on the third day and the bilirubin quite high, (over 24.5 mgm.%) on the fourth day. An exchange transfusion was performed which reduced the serum bilirubin. Only one exchange transfusion was necessary. There was no indication as to the cause of hyperbilirubinemia, although I would take exception to the protocol which states that there was no sign of sepsis. Jaundice itself is one of the best signs of sepsis, and recent studies published in the *Pediatric Clinics of North America* indicate that while respiratory distress is the leading manifestion of sepsis, it is closely followed by jaundice as a clinical manifestation of sepsis in the newborn. In such instances, there are probably cumulative factors which lead to hyperbilirubinemia, the most important probably being immaturity of liver function.

*Associate Professor, Department of Pediatrics, University of Minnesota Medical School.

Blood and spinal fluid cultures in this infant were negative, and this would seem to exclude bacteria as a cause of sepsis since negative blood cultures are infrequent in infantile sepsis.

The mother was given a complimentary pack of six cans of ready-to-serve formula and one pack of concentrated formula when the infant was discharged. The weight was normal on discharge. On the first day following discharge, he was given six small bottles of formula (24 ounces) which is not excessive and which in no way suggests diabetes insipidus. This was followed by the concentrated formula without the necessary dilution having been made. Prepared formulas are generally designed to simulate human milk and even when undiluted have protein, fat, carbohydrate, and mineral contents which are quite similar to cows milk (Table).

TABLE

Preparation	Protein	Fat	Carbohydrate	Minerals
Human	1.25%	3.5%	7.5%	.15%
Cow	3.5	3.5	4.7	.54
Similac	3.5	7.8	1.3	.75
Bakers	4.3	6.4	1.3	1.2

The infant apparently got only one bottle of the concentrated formula. The mother subsequently noted the diapers were consistently dry, and since this event took place in July, normally a hot month even in Minnesota, dehydration due to sweating from external heat could well have been an important contributing factor in this infant's dehydration.

During the second day at home he became irritable, developed respiratory distress, apparently aspirated, became cyanotic and was brought to the Emergency Room. Examination at that time revealed him to be cyanotic and in obvious shock with respirations of 100, a heart rate of 60, a rectal temperature of 102°, an unobtainable blood pressure, and poor peripheral circulation. The infant was moribund for all practical purposes, and neurologic examination revealed absent pathologic reflexes, jerky, purposeless movements, and increased tone. He had sustained a marked weight loss amounting to 12% of his body weight on discharge two days previously. Since his diapers had been consistently dry, it would seem that he had become dehydrated principally through sweating and increased respiration.

Several possibilities could be considered at this time which would be compatible with the history and clinical course. Birth injury cannot be excluded. It is also quite possible that this infant had a congenital infection even though the blood cultures were sterile. Organisms which do not grow on ordinary media are Toxoplasma or cytomegalic virus. The central nervous system signs this infant presented are compatible with infections with these organisms. One might also consider the possibility of a renal tubular abnormality with subsequent loss of fluids, inability to exchange ions, and concomitant retention of sodium and chloride. The electrolyte studies would be consistent with tubular acidosis or absence of antidiuretic hormones with associated diabetes insipidus.

On admission to the hospital, the infant was hydrated with initial improvement in heart rate and serum electrolytes, increased urinary flow and improved color. Signs of central nervous system damage persisted, however, characterized by irritability, a high pitched cry and tremulous movements of extremities.

It is quite possible that a combination of both increased electrolytes received in the concentrated formula together with excessive sweating culminated in

the dehydration and hypertonicity observed clinically. The irreversible downhill course in the hospital was probably on the basis of central nervous system damage and renal damage occurring during the shock episode. The etiology of shock, however, may have some other basis than dehydration. Neonatal sepsis is somewhat suggested by the history of premature ruptured membranes, subsequent unexplained hyperbilirubinemia, and antibiotic coverage following the exchange transfusion; but, with sterile cultures, such sepsis seems to be excluded. Cytomegalic virus infection or Toxoplasma infection is also a possibility. Serum levels of IgM in neonates may be helpful clues in the diagnosis of intrauterine fetal infection. Sera from newborns with IgM levels greater than 20% of the gamma globulin level are highly suggestive of previous intrauterine infection. It would seem that this procedure may be a helpful diagnostic measure in babies with unexplained jaundice.

Clinical Diagnoses

1. Probable central nervous system cytomegalic disease
2. Hypertonic dehydration
3. Secondary renal tubular acidosis

Pathology Discussion

Dr. Anderson:

Postmortem examination disclosed no evidence of sepsis, and, in particular, there were no changes suggestive of cytomegalic inclusion disease or toxoplasmosis. Findings, however, were those of a severe dehydration with its resultant complications. A definitive pathogenesis for this was not established, though probably a combination of excessive sweating together with intake of undiluted formula led to the state of dehydration and hypertonicity. At the time of hospitalization, central nervous system lesions were undoubtedly extensive and irreversible in spite of some initial improvement in the clinical course. The brain was the organ of most severe involvement, disclosing extensive engorgement and thrombosis of the major dural sinuses and intracerebral veins. There was extensive engorgement with virtually complete thrombosis of the superior sagittal sinus associated with focal hemorrhage into the adjacent falx cerebri. The major draining sinuses and

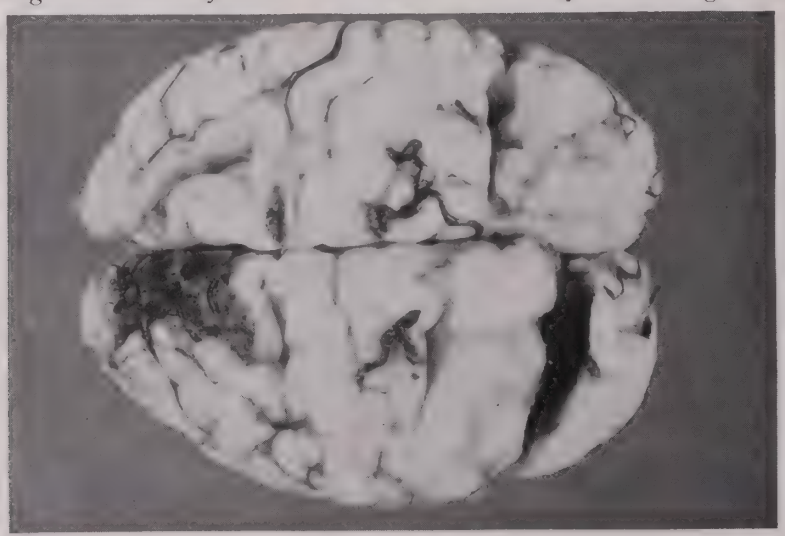


Fig. 1—Cerebral convexities showing distended thrombosed cortical veins and subarachnoid hemorrhage over the left superior frontal lobe.

cortical veins over the cerebral convexities also disclosed marked venous stasis and recent thrombosis. There was an extensive area of subarachnoid hemorrhage over the left superior frontal lobe that extended medially into the longitudinal cerebral fissure (Figure 1). Recent subarachnoid hemorrhages were also present bilaterally over the inferior cerebellar surfaces, and sectioning disclosed extensive hemorrhage throughout the ventricular system. The white matter of both cerebral hemispheres was the site of extensive necrosis of venous drainage areas characterized by widespread softening, cavitation, and hemorrhage into adjacent neural parenchyma (Figure 2). In these areas, venous engorgement and thrombosis were quite prominent. There was softening of the corpus collosum, and hemorrhagic softening of the internal capsule, caudate nuclei and thalamic nuclei bilaterally. The marked venous engorgement, stasis, distention, and early thrombosis of dural sinuses and intracerebral veins were confirmed in microscopic studies (Figure 3). Areas of venous infarction were characterized by dissolution and rarefaction of white matter, focal capillarization, and reactive astrocytosis.

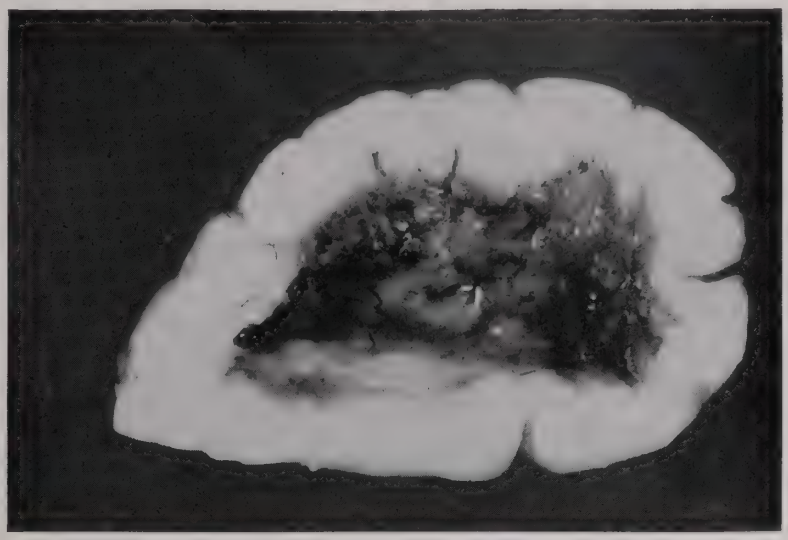


Fig. 2—Coronal section of cerebral hemisphere showing large cavitated area of necrosis involving white matter.

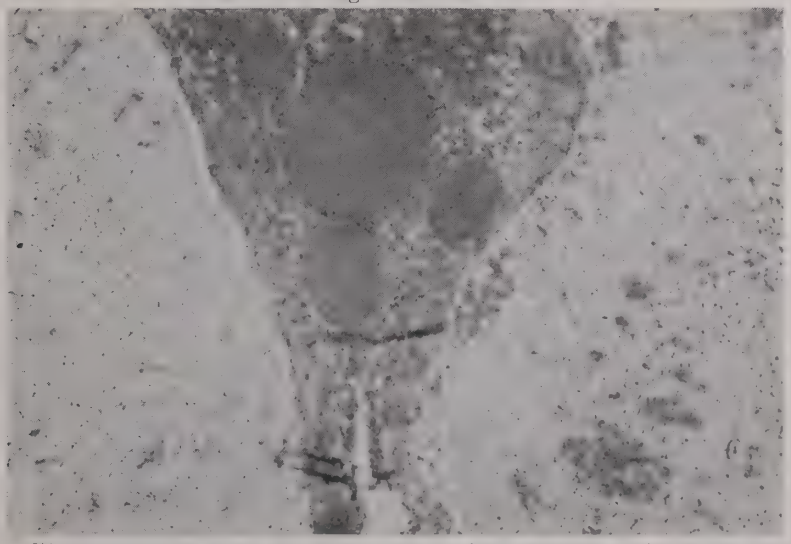


Fig. 3—Representative cerebral sulcus in which there is stasis and thrombosis of cortical veins, subarachnoid hemorrhage and focal cortical hemorrhages. Hematoxylin and eosin. x20.

Examination of other systems disclosed striking microscopic changes in the thymus, kidney and parotid gland. The thymus weighed 5 grams, whereas normal weight for this size infant would be 12 to 13 grams. Marked thymic involution was present, evidenced by a uniform depletion of cortical lymphocytes. These changes may be associated with sepsis, stress and dehydration, and probably the latter factors were both cumulative in this instance. The kidneys disclosed no abnormalities on gross examination. Microscopically, however, there was an extensive acute necrosis of proximal renal tubules that was attributed to both dehydration and shock with subsequent decreased renal blood flow (Figure 4). The parotid gland also showed effects of dehydration characterized by an acute sialadenitis with areas of interstitial inflammation and inflammatory destruction of acini. The lungs were not notably altered grossly, but microscopically did disclose pulmonary edema and an acute alveolitis, undoubtedly the precursor to a pneumonitis that would have ensued with longer survival.

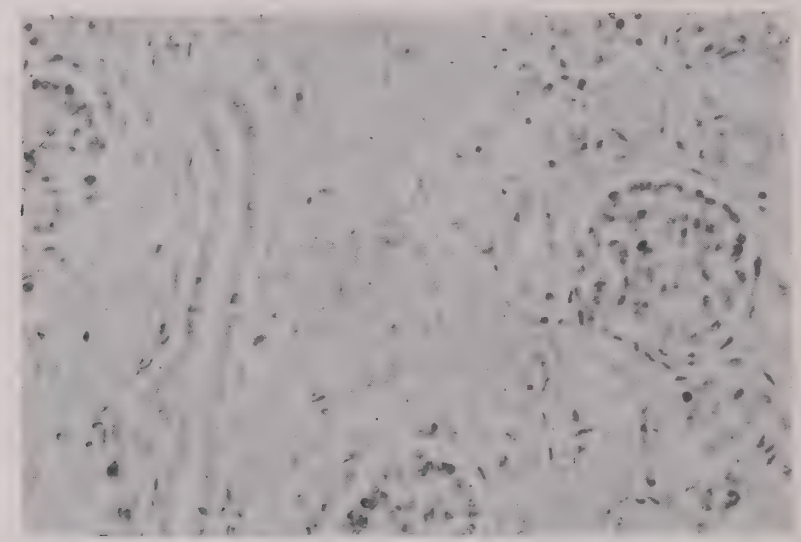


Fig. 4—Acute renal tubular necrosis in which proximal tubules are filled with desquamated granular necrotic lining epithelium. Hematoxylin and eosin. x50.

This case is illustrative of the not infrequent observation that subarachnoid and/or subdural hemorrhage may occur in states of dehydration with hypernatremia. Most observers attribute these changes to brain shrinkage and distortion. It is recognized that with hypertonicity, changes in brain size with shrinkage together with reduction in cerebrospinal volume and pressure do occur.[1-3] Furthermore, vessels in the brain receive some mechanical support from the surrounding neural parenchyma. With shrinkage this natural support is decreased; consequently these vessels may have increased liability to damage. It has been suggested that these factors are probably operative in hypertonic dehydration resulting in parenchymal shrinkage with secondary shearing and tearing of delicate bridging veins leading to subsequent subarachnoid and subdural hemorrhages.

A further point of interest is the frequent association of neurologic sequellae with states of dehydration and hypernatremia. In this particular instance, it is easy to relate neurologic symptoms with the widespread destructive lesions in the central nervous system. However, dehydration with hypernatremia has been frequently associated with neurologic symptoms in which there are no appreciable correlative anatomic findings.

Clinical and experimental studies suggest that in such instances there may be a biochemical derangement within the neuron due to cellular desiccation and to the formation of idiogenic osmols secondary to the breakdown of bound electrolytes.[1,2] In addition, hypocalcemia has also been observed in some instances of hypernatremic dehydration. Although its pathogenesis is not clear, nevertheless, this may further contribute to hyperirritability and other neurologic symptoms.[4]

Final Anatomic Diagnoses

1. Hypertonic dehydration with marked hypernatremia
2. Secondary thrombosis of dural sinuses and intracerebral veins with venous infarctions of cerebral hemispheres
3. Subarachnoid and intraventricular hemorrhages
4. Acute renal tubular necrosis
5. Acute sialadenitis
6. Involution of thymus

W. Robert Anderson, M.D.*
Paul G. Quie, M.D.**
Minneapolis, Minnesota

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**Associate Professor, Department of Pediatrics, University of Minnesota Medical School.

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Darwin on Communal Society*

"The perfect equality among the individuals composing the Fuegian tribes,** must for a long time retard their civilization. As we see those animals, whose instinct compels them to live in society and obey a chief, are most capable of improvement, so it is with the races of mankind. Whether we look at it as a cause or consequence, the more civilized always have the most artificial governments. For instance, the inhabitants of Otaheite,† who, when first discovered, were governed by hereditary kings, had arrived at a far higher grade than another branch of the same people, the New Zealanders—who, although benefited by being compelled to turn their attention to agriculture, were republicans in the most absolute sense. In Tierra del Fuego, until some chief shall arise with power sufficient to secure any acquired advantage, such as the domesticated animals, it seems scarcely possible that the political state of the country can be improved. At present, even a piece of cloth given to one is torn to shreds and distributed; and no one individual becomes richer than another. On the other hand, it is difficult to understand how a chief can arise till there is property of some sort by which he might manifest his superiority and increase his power."—Stewart Lane Arey, M.D.

*Charles Darwin—The Voyage of the Beagle. Doubleday & Co., Inc., Gorgen City, New York, 1962.
**Indians from the island of Tierra del Fuego at the tip of South America, belonging to Chile.
†Former name for Tahiti.

It's the Law

Suit Against Hospital for Breach of Express Warranty in Furnishing Contaminated Blood Dismissed*

A suit for damages against a hospital by the husband of a patient who died from serum hepatitis after she received a blood transfusion in the course of prenatal care was properly dismissed by trial court. The husband claimed that blood, administered by a hospital, carried an express and implied warranty of purity. After receiving the blood the patient developed serum hepatitis and expired.

The rule, developed in prior cases against hospitals for damages for breach of implied warranty for having furnished contaminated blood, was applicable. A hospital's furnishing of blood for transfusion is termed a "service," not a "sale." Since there is no "sale," there is no cause of action for breach of warranty.

*Case Reference—Payton v. Brooklyn Hospital, 224 N. E. 2d 891 (N. Y., January 19, 1967) "The Citation" Vol. 15, No. 6, June 30, 1967.

All You Had to do Was to Take Stock of Yourself

I sat down with paper and pencil to plot my future . . . I tried to go back over my life and recall one useful thing I had done well and enjoyed doing, to dislodge from the debris of ineptitude a single small splinter of natural ability with which to prick my way into a career that would mean stability, security, and self-respect.

In turning back the pages I came eventually to Mr. Stilts. Mr. Stilts was a snow-white stork of entrancing ungainliness which had been given to me for my tenth birthday. Until the Revolution separated us Mr. Stilts and I were devoted companions during the summer vacations which I spent on our estate near Minsk. We both found the same delight in wading knee-deep in the marshy edges of a near-by stream and splashing muddy water up to our necks. He had a great flair for sticking his long neck and legs into the places it was unhealthy for a stork to be. My mother made quite a moral of it when as the result of straying he was carried home one day with a broken leg. I was in no mood for morals. Mr. Stilts was in trouble. For all I knew Mr. Stilts was dying.

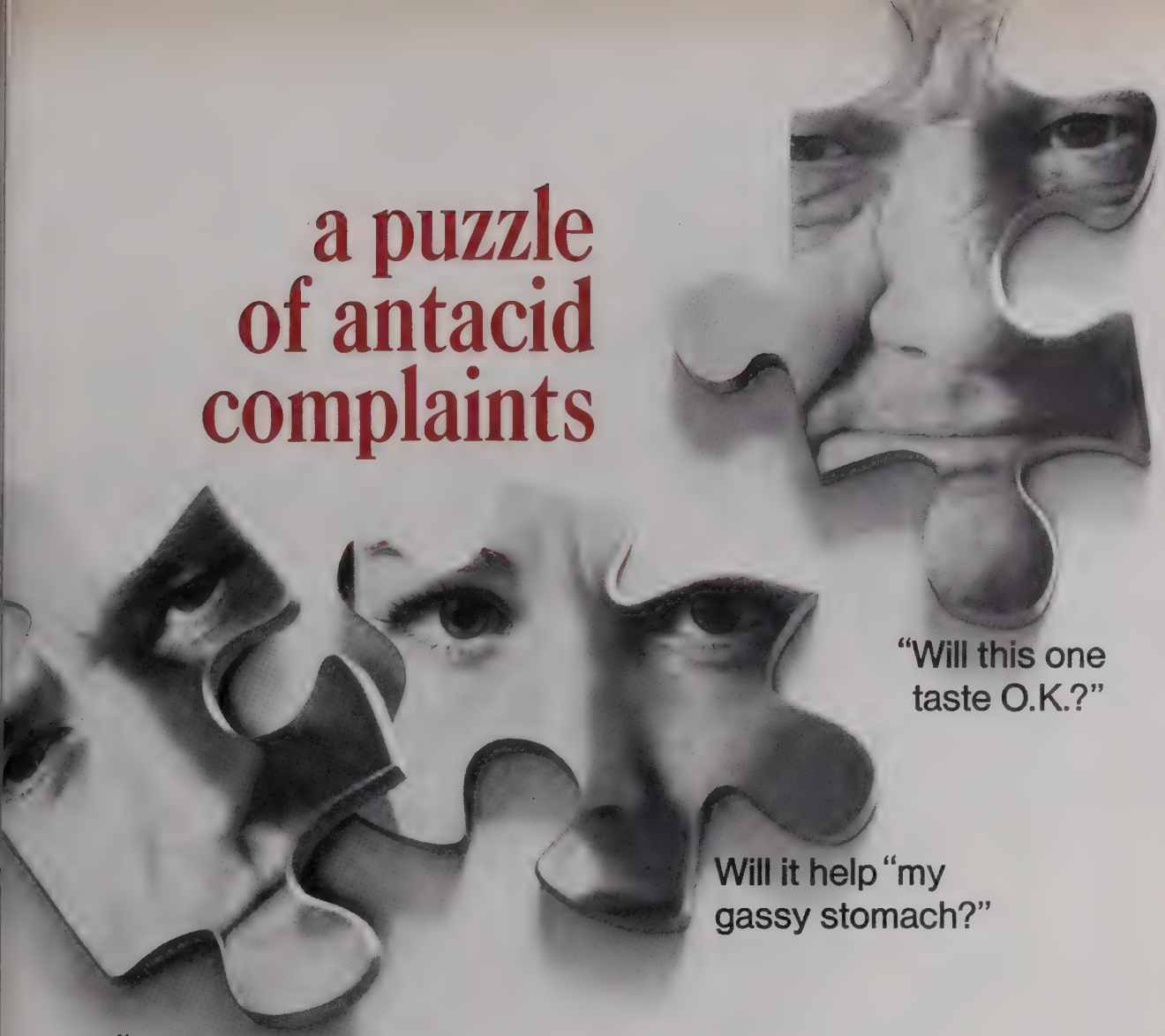
I gathered Mr. Stilts up in my arms and ran with him to a shed some distance from the barn. There I laid him on a box and examined the leg to find the two ragged ends of bone. With infinite care I pressed them together and bound the leg rigid with splints cut from an old board and bandages extracted from my undershirt. In two weeks Mr. Stilts was as good as new.

It had been years since I had thought of my youthful career as an animal doctor, but in remembering it at long last I could still recapture a little of the thrill of success when Mr. Stilts came out of his bandages whole and without a limp. That was something I had done well and enjoyed doing. This great American game of planning one's future was beginning to make sense. There was nothing to it once you found the formula. All you had to do was to take stock of yourself, find the thing you would like doing, and then let nothing stand in the way of doing it.*

*Eugene de Savitsch (1903-) in Why We Became Doctors, edited by Noah D. Fabricant, M.D., 1954.

Editor's Note: Eugene de Savitsch practiced surgery in Washington, D. C.

a puzzle of antacid complaints



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a solution to peptic ulcer distress

Effective neutralization—
with the two most widely prescribed antacids: aluminum and magnesium hydroxides.

Concomitant relief of G.I. gas distress—
with the proven[1] defoaming action of simethicone.

Prolonged acceptance confirmed—
in 87.5% of 104 patients after a total of 20,459 documented days of therapy.[2]

Composition: Each Mylanta chewable tablet or teaspoonful (5 ml.) contains: magnesium hydroxide, 200 mg.; aluminum hydroxide, dried gel, 200 mg.; simethicone, 20 mg. Dosage: One or two tablets (well chewed or allowed to dissolve in the mouth) or one or two teaspoonfuls to be taken between meals and at bedtime.

References: 1. Hoon, J.R.: Arch. Surg. *93*:467 (Sept.) 1966.
2. Danhof, I.E., Personal communication.

Stuart Division/Pasadena, Calif.
ATLAS CHEMICAL INDUSTRIES, INC.

new evidence for TAO® (triacetyl-oleandomycin)

a macrolide antibiotic for the frequently seen respiratory infection in the office and for a problem pathogen* in the hospital.

*Staphylococcus aureus

study I[1]

Results of a 1967 **in vitro—in vivo** correlation study involving 116 patients with Gram-positive coccal infections in five institutions. All patients were given TAO prior to determining the susceptibility of the offending organism.

97.0%
of the organisms were susceptible to oleandomycin*

98.0%
of the patients responded favorably to TAO® (triacetyloleandomycin)

*In some cases more than one pathogenic organism was isolated from the patient.

study II[2]

Effect of oral therapy with TAO, erythromycin, and cloxacillin on the survival time of Rhesus monkeys after intravenous inoculations of lethal doses of staphylococci, phage type 80/81. (8 monkeys in each group)

conclusion:

*Under the conditions of this study and the doses employed, it was found that

TAO® (triacetyl-oleandomycin)

was far superior to erythromycin, as was cloxacillin, a bactericidal agent, and of particular interest, "...bacteriostatic triacetyloleandomycin was as effective or perhaps superior to cloxacillin in preventing lethal (staphylococcal, phage type 80/81) infection."

*It should be pointed out that results obtained in an experimental study of this nature may not necessarily be directly extrapolated to the clinical situation as it pertains to man.

TAO Rx Information

INDICATIONS: Include streptococci, staphylococci, pneumococci and gonococci. Recommended for acute, severe infections where adequate sensitivity testing has demonstrated susceptibility to this antibiotic and resistance to less toxic agents. **CONTRAINDICATIONS AND PRECAUTIONS:** Not recommended for prophylaxis or in the treatment of infectious processes which may require more than ten days continuous therapy. In view of the possible hepatoxicity of this drug when therapy beyond ten days proves necessary, other less toxic agents should be used. If clinical judgement dictates continuation of therapy for longer periods, serial monitoring of liver profile is recommended, and the drug should be discontinued at the first evidence of any form of liver abnormality. When treating gonorrhea in which lesions of primary or secondary syphilis are suspected, proper diagnostic procedures, including darkfield examinations, should be followed. In other cases in which concomitant syphilis is suspected, monthly serological tests should be made for at least four months. Contraindicated in pre-existing liver disease or dysfunction, and in individuals hypersensitive to the drug. Although reactions of an allergic nature are infrequent and seldom severe, those of the anaphylactoid type have occurred on rare occasions. When used in streptococcal infections, therapy should be continued for ten days to prevent the development of rheumatic fever or glomerulonephritis. The use of antibiotics may occasionally permit overgrowth of nonsusceptible organisms. A resistant infection or superinfection requires re-evaluation of the patient's therapy. In the event such occurs with this drug the medication should be discontinued, and specific antibacterial and supportive therapy instituted.

References: 1. Isenberg, H. D.: Clinical Evaluation of Laboratory Guidance to Antibiotic Therapy; Health Laboratory Science (July) 1967. 2. Saslaw, S., Carlisle, H. N.: Studies on Therapy of Staphylococcal Infections in Monkeys. 1. Comparison of Cloxacillin, Triacetyloleandomycin and Erythromycin. Proc. Soc. Exp. Biol. & Med.: Vol. 125, No. 4 (Aug.-Sept.) 1967.

ROERIG Rx
J. B. ROERIG DIVISION
CHAS. PFIZER & CO., INC.
235 EAST 42nd STREET
NEW YORK, N.Y. 10017

For your impatient cold patients

Two sprays from NTZ Nasal Spray—and nasal congestion, rhinorrhea, sneezing are reduced for *immediate* comfort for patients with colds.

NTZ is more than a simple vasoconstrictor. It contains:

Neo-Synephrine® **(brand of phenylephrine) HCl 0.5 per cent,** the major component, virtually synonymous with fast, efficient but gentle nasal vasoconstriction on contact.

Thenfadil® **(brand of thenyldiamine) HCl 0.1 per cent,** topical antihistamine for reduction of rhinorrhea, sneezing or itching. It combats the allergic reactions that may occur in colds or sinusitis.

Zephiran® **(brand of benzalkonium, as chloride, refined) 1:5000,** antiseptic preservative and wetting agent to promote penetration and spread of the formula.

NTZ is well tolerated. Used in a cold it may help prevent sinusitis by opening sinus ostia and permitting drainage. It may also be used in sinusitis to help establish drainage.

The spray is best used twice, the second a few minutes after the first, repeated every three or four hours as needed. NTZ is for temporary relief of nasal symptoms, and overdosage should be avoided.

Supplied: NTZ Nasal Spray, plastic squeeze bottles of 20 ml.; NTZ Nasal Solution, bottles of 30 ml. (1 fl. oz.) with dropper.

Winthrop

Winthrop Laboratories
New York, N.Y. 10016



NTZ®
NASAL SPRAY

relieves
nasal symptoms
on contact

Advance

Use of Lithium Carbonate in Private Psychiatric Practice

MOST DOCTORS well remember a disheveled, bizarrely-attired patient, bleary-eyed from lack of sleep, unable to sit still because of a frenzy of activity, and speaking in a flurry of words about grandiose personal plans. Treatment for this manic patient usually includes tranquilizers and/or electro-convulsive therapy. Tranquilizers often result in a rigid, lethargic patient who stays in the hospital for several months until the natural course of the attack is complete. Electro-convulsive therapy may result in a quicker recovery but is complicated by partial memory loss. These treatments are particularly detrimental to patients who need factual information to adequately perform their job and cannot afford to miss much work.

Early Use of Lithium Therapy

Within the past decade lithium salts have been popularized as a new therapy for this manic state. Cade's 1949 discovery that the lithium ion can erase endogenous excitement[1] found wide acceptance outside of the United States. Eighteen studies from 1954 to 1960 report 80-90% improvement in 370 manic patients treated with lithium.[2] Reports indicate that maintenance of lithium blood levels act as prophylaxis against recurring manic or depressive attacks.[3] Only recently have American psychiatrists tried the drug and recorded their favorable results.[2,4]

Establishment of Lithium Treatment in Minnesota

In 1955 Northwestern Hospital in Minneapolis began performing serum lithium determinations and dispensing 300-mgm. lithium carbonate capsules. These efforts were initiated by the author to provide lithium treatment for manic patients in the Twin Cities area. At the current time lithium carbonate is under thorough investigation, and physicians using it are requested to claim investigational exemption authorized by the Food and Drug Administration. The lack of physician familiarity with lithium carbonate in the treatment of manic disorders prompted the preparation of this paper, based on the author's experience with 15 patients.

Initial Treatment Procedure

The first step should be confirmation of the diagnosis of the manic state. The individual may suffer from organic illness or drug abuse. After the manic diagnosis is made, the patient should be hospitalized before the doctor begins treatment with lithium carbonate. (In three patients who were treated on an outpatient basis lithium therapy failed because of inadequate control of the patients and the medications.) Outpatient treatment can prove dangerous, as the psychotic patient may misinterpret drug instructions. There is no substitute for hospitalization. Once hospitalized, the patient is evaluated with a thorough examination, particularly as to cardiac and urinary status. Either coronary or kidney damage contraindicate use of the drug. Women of childbearing age are excluded to avoid possible fetal damage.

Control of Lithium Dosage

The selected patient is begun on 300 mg.

lithium carbonate capsules, t.i.d., given with meals to decrease any initial nausea and gastric distress. (One patient declined lithium because of this distress.) Most patients tolerate a rapid build-up of medication to the point of two capsules, t.i.d., or 1800 mg. of lithium carbonate per day. They are continued on this level until either their serum lithium level approaches 1.8 meq./liter or the manic attack "breaks." The latter phenomenon is comparable to a fever crisis before the antibiotic period and occurs usually within a week. To adequately control the patient until the serum lithium increases, sedative drugs are given. Thorazine or Taractan may be necessary up to 800 mg. per day during the first week, but then can be decreased rather rapidly. Patients are notified that lithium may cause gastric distress, fine tremors of the hands, and some sleepiness. They are advised to salt their food regularly to help prevent toxic build-up of the lithium salts.

Monitoring Lithium Levels

Serum lithium tests are started about four days after beginning the drug and should be performed at least twice a week. If the patient becomes clinically toxic with excessive somnolence, ataxia and slurred speech, serum lithium levels should be done more frequently. Levels are therapeutic between 1.5 and 1.8 meq./liter. Levels lower than this will probably not "break" the manic attack and levels higher approach a dangerous toxic range. Clinical impressions do not always correlate with the lithium level; therefore laboratory tests are essential. If toxic symptoms appear and the lithium level approaches 1.8 meq./liter, discontinuing the lithium for one or two days will bring the level under control. When the manic attack "breaks" the patient quickly becomes sensitive to the lithium. The dosage has to be decreased rapidly to one capsule, t.i.d. or q.i.d.; otherwise there is toxic danger to the patient. As the patient returns to a normal affective level a maintenance amount of lithium should be given. About three capsules per day will maintain him at a baseline of about 1 meq./liter, will provide safety from toxicity, and is at the level suggested to prevent recurrence of manic episodes.

Aftercare Treatment of Patient and Family

Much cooperation from the patient and his family is necessary for long-range success.[5] Individuals who resist medication and will not cooperate on drug programs should be handled by other treatment. Before a patient is released from the hospital a conference should be held with him and his family. At this time the danger signs of impending mania are discussed. Each individual has mannerisms which are clues to an impending manic attack. Thorough discussion of these clues familiarizes the family with these danger signs. The family and the patient will be instructed to call the doctor immediately if any of the mannerisms appear. The patient should be informed that a doctor's request at that time to go into a hospital and/or increase the lithium should be followed, even though the patient may not feel it is necessary. Also at the conference signs of lithium toxicity should be discussed with the family so that they will call the doctor in case of dangerous build-up of lithium salts.

Results of Treatment

Of the 15 study patients treated with lithium carbonate, 14 were manic-depressive patients, manic type. The other was a manic-depressive psychotic, depressed type, who suffered a recurring depression despite maintenance therapy with lithium carbonate. Three other treatment failures were study patients treated as outpatients. Poor medication control appears significant in their lack of improvement. All 11 patients hospitalized and adequately treated with lithium carbonate had their manic attack "break" within two weeks of beginning controlled treatment. Unfortunately two patients have had recurrent attacks despite maintenance lithium carbonate therapy. The second attack was adequately treated by hospitalization and increase of dosage. In three study individuals who became hypomanic on maintenance therapy, an increase of dosage aborted the attack and prevented hospitalization. Ten of the study patients continue on maintenance therapy. No serious side-effects have appeared and no discontinuation of medication has been necessary.

Summary

Lithium therapy in manic attacks is a new

mode of treatment which was successful in terminating manic attacks in all 11 patients hospitalized and adequately treated with lithium carbonate. It appears to offer a new range in therapy without the oversedation of tranquilizers and the forgetfulness of electroshock therapy, and without a prolonged hospitalization for the patient. Careful adherence to hospitalization, dosage schedule, and serum lithium tests is necessary for successful therapy. Otherwise dangerous toxic side-effects may jeopardize the patient's health. Selective use of lithium carbonate in private psychiatric practice appears beneficial and safe in treating manic patients.

William Brauer, M.D.
Minneapolis, Minnesota

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3. Baastrup, P. C., Schou, M.: Lithium as a Prophylactic Agent; It's Effect against Recurrent Depressions and Manic-Depressive Psychosis. Arch Gen Psychiat 16:162, 1967.
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Mr. President—Your Health*

John Quincy Adams (1767-1848)

Deliberately and unremittingly imposing upon himself a regimen of walking, swimming, horseback riding and moderation, our sixth President, John Quincy Adams, kept himself physically fit right up into middle age. Despite good health, however, he was plagued with misgivings about his constitutional stamina. He complained of insomnia: "I get but five hours a night of disturbed sleep—full of tossings." Also he was unduly discouraged by bouts of laryngitis which impaired his public-speaking voice.

While Adams was a congressman, his health finally registered the full impact of over-strenuous and conscientious public service; one day after leaving the House he fell precipitately to the floor, gashing his forehead and dislocating a shoulder, the agonizing reduction of which took over an hour in time and stoic endurance on Adams' part. Whether he tripped on a mat or was the victim of a slight stroke was never determined; but thereafter his vision began to weaken and his hand to shake, symptoms he regarded as premonitory of final dissolution.

After a genuine stroke from which he only partially recovered, he was wont to reply with serene detachment to all queries about his health: "John Quincy Adams himself is quite well, thank you. But the house in which he has been living is now dilapidated. It totters on its foundations. Time and the seasons have nearly destroyed it. The walls are shattered, and the building trembles in every wind. Before long, John Quincy Adams will have to move out. But he himself is quite well."

One day at the age of eighty he collapsed in the House. Physicians tried to restore him by cupping, bleeding, poulticing, leeching, and rubbing—all to no avail. Under the dark shadow of death he recovered consciousness only sporadically, and his final words were: "This is the last of earth! I am content."

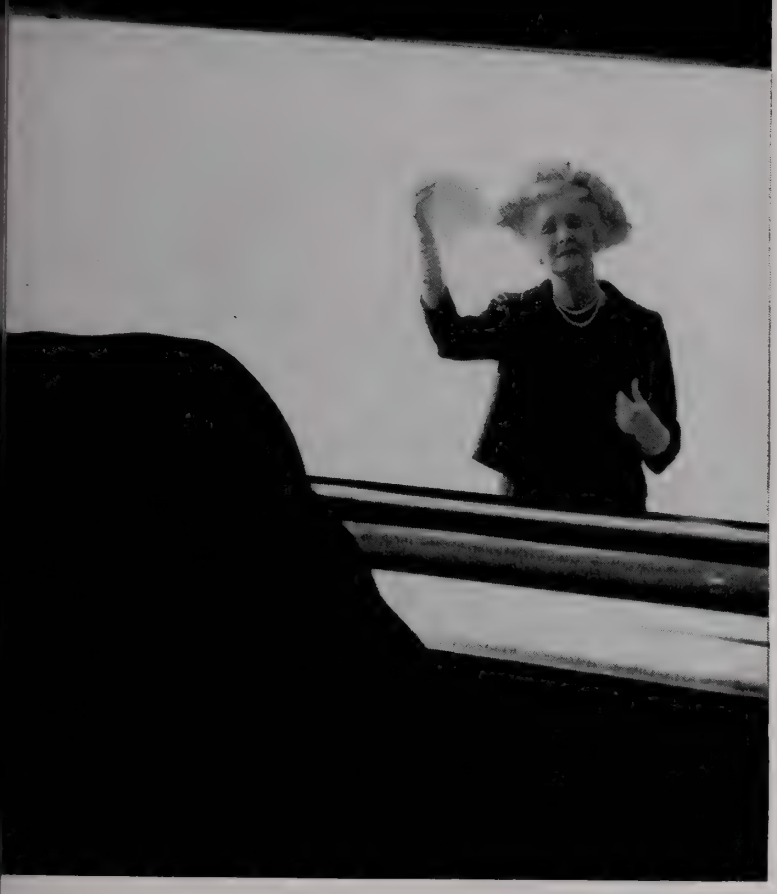
*With acknowledgements to Karl C. Wold, M.D.: Mr. President—How Is Your Health?

Perhaps we would never do all we do without the hope of doing more than we can.—Bernard de Fontenelle



Indications: Tofrānil is recommended for the treatment of depressive states of diverse psychopathology.
Contraindications: The concomitant use of Tofrānil and monoamine oxidase inhibiting (M.A.O.I.) compounds is contraindicated. Hyperpyretic crises or severe convulsive seizures may occur. Potentiation of adverse effects can be serious or even fatal. An interval of at least 7 days after M.A.O.I. therapy has been discontinued should be allowed before Tofrānil may be substituted. Initial Tofrānil dosage should be low, increases should be gradual, and the patient's progress should be carefully observed.
Warning: Clinical reports have suggested that there may be a risk of teratogenesis associated with the use of this compound during the first trimester of pregnancy. Unless, in the opinion of the prescribing physician, the potential benefits outweigh the possible risks, Tofrānil should not be used during the first trimester of pregnancy.
Cardiovascular complications, including myocardial infarction and arrhythmias, have occasionally occurred in susceptible individuals. Patients with cardiovascular disease should be given the drug only under careful observation and in low dosage.
Precautions: Since suicide is always a possibility in severely depressed patients and one which may persist until significant remission occurs, such patients should be carefully supervised during early treatment with Tofrānil. Some severely depressed patients may also require hospitalization and/or concomitant electroconvulsive therapy.
Because of its anticholinergic effect, caution should be observed in prescribing Tofrānil for patients with increased intraocular pressure.
In rare instances, transient cardiac arrhythmias have occurred in hyperthyroid patients and in patients receiving thyroid medication when Tofrānil was added to the regimen.
Imipramine may block the pharmacologic activity of guanethidine and other related adrenergic neuron-blocking agents.
The drug is not recommended at the present time in patients under 12 years of age.
Adverse Reactions: Dryness of the mouth, tachycardia, constipation, disturbances of accommodation, sweating, dizziness, weight gain, urinary frequency or retention, nausea and vomiting, peripheral neuritis, mild parkinson-like syndrome, tremors, rare cases of falling in elderly patients, confusional states (with such symptoms as hallucinations and disorientation), activation of psychosis in schizophrenics and agitation (includ-

When a milestone in life is marred by depression...



Often in the mind of the lonely, widowed, depression-prone individual, she's not gaining a daughter...she's losing a son. The occasion may be marred by such symptoms of depression as feelings of sadness, incapacity, helplessness and hopelessness.

In about 3 out of 4 cases, Tofrānil relieves symptoms of primary depression.

As maintenance therapy in primary depressive illness, it helps prevent relapse.

Although toxic reactions severe enough to require discontinuation of Tofrānil are uncommon, in patients with cardiovascular disease, thyroid disorders, increased intraocular pressure, or in those receiving anticholinergics (including antiparkinsonism agents), the special precautions listed in the Prescribing Information should be carefully observed. The use of Tofrānil in patients receiving M.A.O.I.'s is contraindicated.

Tofrānil® imipramine hydrochloride Geigy

ing hypomanic and manic episodes) which may require dosage reduction and/or addition of a tranquilizer or temporary discontinuation of the drug, epileptiform seizures, orthostatic hypotension and substantial blood pressure fall in hypertensive patients, purpura, transient jaundice, bone marrow depression including agranulocytosis, sensitization and skin rash including photosensitization, eosinophilia, and mild withdrawal symptoms on sudden discontinuation after prolonged treatment with high doses. Occasional hormonal effects (impotence, decreased libido, and estrogenic effects) may be observed. Atropine-like effects may be more pronounced (e.g. paralytic ileus) in susceptible patients and in those using anticholinergic agents (including antiparkinsonism drugs).
Outpatient Adult Dosage: Initially, 75 mg. daily, increased, if necessary, to 150 or 200 mg. Maintenance dosage may be lower, 50 to 150 mg. daily, if possible.
Geriatric and Adolescent Dosage: Initially, 30 or 40 mg. daily, which may be increased according to response and tolerance. It is usually unnecessary to exceed 100 mg. daily.
A lag in therapeutic response, lasting from a few days to a few weeks, should be expected. When dosage recommendations are already being followed, increasing the dosage does not normally shorten this latency period and may increase the incidence of adverse reactions.
Availability: Tofrānil: Round tablets of 25 and 50 mg.; triangular tablets of 10 mg. for geriatric and adolescent use; and ampuls, each containing 25 mg. in 2 cc. for I.M. administration.
(B)46-850-C
For complete details, please refer to the full Prescribing Information.

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Dermatology

Melasma (Chloasma)

PIGMENTATION WHEN irregular in nature or unequal in intensity is cosmetically objectionable to many patients, men as well as women. The term melasma is used in a restricted sense to describe hyperpigmentation occurring in pregnancy, in menopause, with ovarian disorders, and with the use of oral contraceptives. It has also been reported in patients receiving hydantoin preparations. In pregnancy the areas most frequently involved are the face, areolae of the nipples, external genitals and the linea alba. Melasma varies in intensity and usually decreases after pregnancy. Melanin is responsible for this pigmentation and in pregnancy is probably due to the increased pituitary melanocyte-stimulating hormone circulating in the body. The mechanisms whereby melanin is increased in the other conditions are not clearly understood. With respect to hydantoin preparations it has been shown experimentally that in fish, at least, this drug has a direct effect consisting of dispersion of melanin and subsequent stimulation of melanin formation. Estrogen and progesterone are strong melanogenic stimulants which probably account for the action of the oral contraceptives in producing melasma-like changes. Of interest is the subjective darkening of the periocular skin and occasionally other areas noted in some women with relation to the menstrual



Figure

cycle. In young women a condition referred to as melasma peribuccale virginum is considered to be related to the tendency to menstrual pigmentation.

It should be noted that chlorpromazine therapy produces darkening due to the deposition of a melanin-like pigment in the dermis. This differs from melasma in that the color is more bluish and the eyes are involved, which is not the case with melasma.

Once the diagnosis of melasma is determined and the etiology clarified, treatment may be instituted, though it is not always successful. Treatment may be divided into three phases. First, removal of the exciting cause if possible. In this area the physician is limited, for in many instances, little can be done, except for the drugs mentioned. Second, an attempt to inhibit the tyrosine-tyrosinase reaction by the use of hydroquinone, which is available for topical application. But this drug must be used with caution, for it can be a potent topical sensitizer. Third, protection from sun exposure which further darkens areas of melasma. This may be achieved by the use of one of the several so-called "sun-screens." The patient should also be advised against such practices as sun-bathing.

In conclusion, it should be mentioned that other causes may be responsible for increased pigmentation, such as post-inflammatory melanosis; melanoderma secondary to malaria, pellagra, diabetes, Addison's disease, metastatic melanoma, to mention a few. All of these should be considered when one sees a patient with increased pigmentation.

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The Progress Notes of Hippocrates

A man, in a heated state, took supper, and drank more than enough; he vomited the whole during the night; acute fever, pain of the right hyponchondrium, a softish inflammation from the inner part; passed an uncomfortable night; urine at the commencement thick, red, but when allowed to stand, had no sediment, tongue dry, and not very thirsty. On the fourth, acute fever, pains all over. On the fifth, urine smooth, oily, and copious; acute fever. On the sixth, in the evening, very incoherent, no sleep during the night. On the seventh, all the symptoms exacerbated; urine of the same characters; much talking, and he could not contain himself; the bowels being stimulated passed a watery discharge with lumbrici:* night equally painful. In the morning had a rigor; acute fever, hot sweat, appeared to be free of fever; did not sleep long; after the sleep a chill, ptyalism; in the evening, great incoherence; after a while, vomited a small quantity of dark bilious matters. On the ninth, coldness, much delirium, did not sleep. On the tenth, pains in the limbs, all the symptoms exacerbated; he was delirious. On the eleventh, he died.—Hippocrates

Editors Diagnosis: Lipid Nephritis

Your Diagnosis: ————————.

*See Test Your Word Score Page 53.

One half the troubles of this life can be traced to saying "yes" too quick, and not saying "no" soon enough.

—Josh Billings

winter 1968

DORSEY Season

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this issue: the cold in pregnancy...

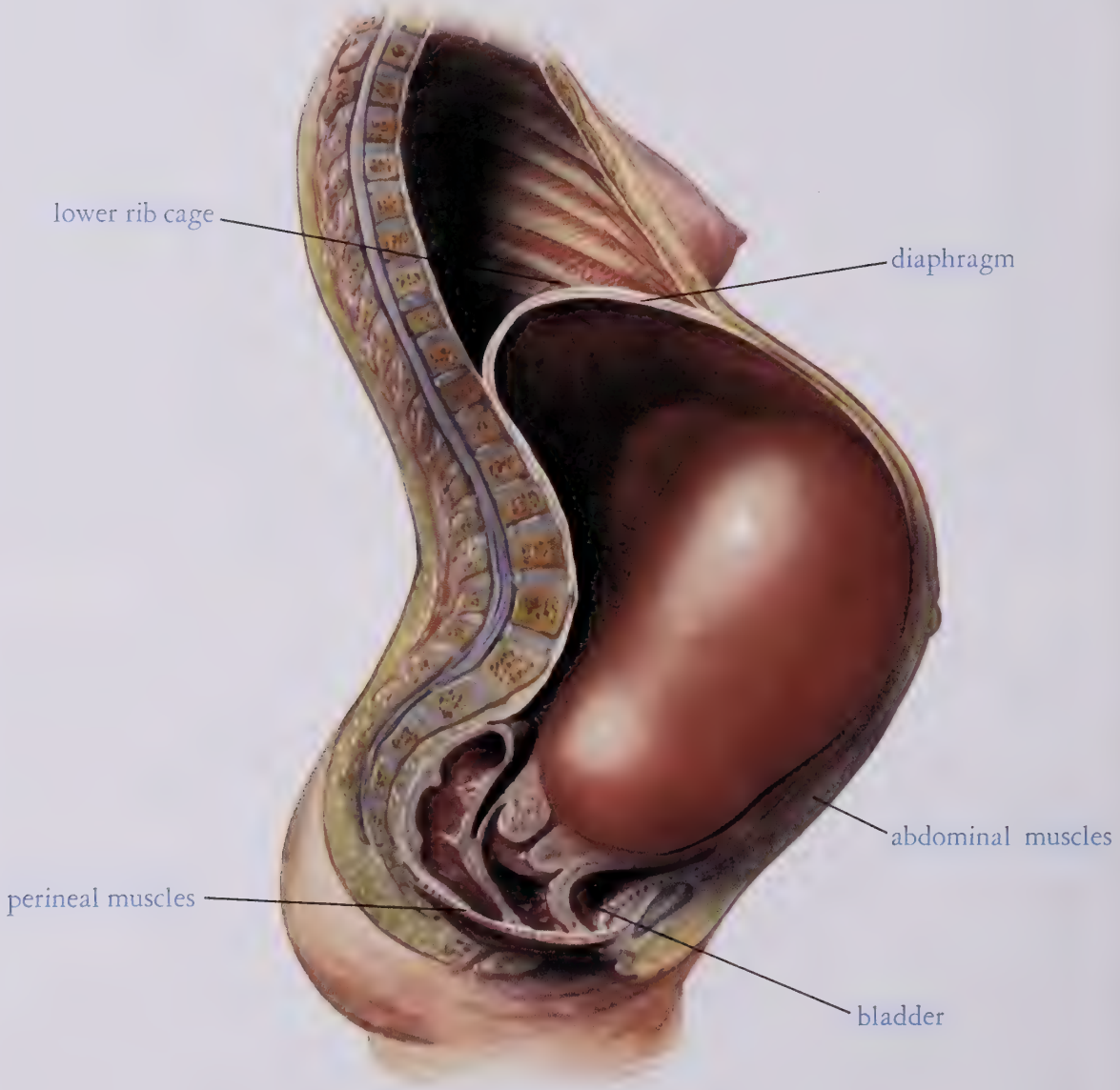
The cold in pregnancy

Frederick W. Goodrich, Jr., M.D.
Senior Obstetrician and Gynecologist, Lawrence and Memorial Hospital, New London, Connecticut

Since pregnancy and the common cold are both ubiquitous, it is not surprising that they often occur at the same time in the same patient. Incidence figures are hard to come by, but the chances are very good that any given pregnant woman will have a cold at some time during the nine months of her gestation. When she does, she will tell you that it is the worst cold she ever had. It seems to last longer and the symptoms are more distressing than they are in the non-pregnant.

For purposes of this discussion, the common cold is considered to be the well-known symptom complex which includes sore throat, stuffy nose, and a cough. Febrile states or extension of the disease process into the lower respiratory tree are not part of the common cold and will not be included in this discussion.

The clinical picture of a cold in pregnancy can be confused by a long-known physiological phenome-



non. Kiesselbach's area in the nose (on the anterior part of the nasal septum above the intermaxillary bone) becomes engorged, apparently due to hyperemia induced by the increased estrogen level which accompanies pregnancy. The amount of congestion can vary in degree from woman to woman. Some have very little congestion, others will have occasional nosebleeds from this area, still others will have symptomatic congestion to the degree that they will complain of having a "chronic" or constant cold.

Less well recognized is the occurrence of this type of hyperemia in any part of the nasopharyngeal mucosa, again in varying degree. Such swelling often produces a postnasal drip which, the patient will state, is present only when she is pregnant. Patients who do not have symptomatic congestion ordinarily, will find that when they do get a cold, the symptoms last much longer than those of a cold usually do. Occasionally, this hyperemia is responsible for closure of the medial end of the Eustachian tube; such patients will complain of "plugging" of the ears. Inspection of the ear drum will show a depression which confirms the presence of Eustachian closure rather than wax in the canal which is the patient's diagnosis. Symptoms related to this physiological congestion are more apt to occur in heavier smokers or those who have a history of allergic rhinitis, just as are the symptoms of the common cold. And when the cold does occur in pregnancy, the symptoms are worse because of the underlying congestion.

The pregnant woman with a cold is miserable for other reasons, dependent somewhat on her parity and the length of her gestation. As parity increases, so also does the relaxation of the abdominal and perineal musculature. The uterus, lying against a slack abdominal wall, and bearing down on relaxed perineal muscles, acts like a piston when the patient coughs, sneezes, or even blows her nose, pushing down on the bladder. Stress incontinence during colds is almost the rule.

As the length of gestation increases, so does the size of the uterus. As it grows, it pushes the abdominal contents above it and elevates the diaphragm. This results eventually in a lateral displacement of the lower rib cage, often to a point at which the patient will complain of soreness in this area. If such a

(Concluded on following page)

From a continuing study on nasal congestion...



timed to work while your patient does

A study begun in 1966 by the Department of Otolaryngology, Greater Baltimore Medical Center, has accumulated evidence that documents the effectiveness of Triaminic's timed-release action in the treatment of nasal congestion.

With its balanced formulation of an oral nasal decongestant and two antihistamines, Triaminic effected partial or complete relief in more than 82% of the 85 subjects treated. Clearing nasal obstruction. Reducing turbinate swelling. Making breathing easier.

It's a comforting thing to know that Triaminic really works.

Triaminic® *timed-release tablets*

Each timed-release tablet contains:

Phenylpropanolamine hydrochloride	50mg.
Pyrilamine maleate	25mg.
Pheniramine maleate	25mg.

Side effects: Occasional drowsiness, blurred vision, cardiac palpitations, flushing, dizziness, nervousness or gastrointestinal upsets. Precautions: The patient should be advised not to drive a car or operate dangerous machinery if drowsiness occurs. Use with caution in patients with hypertension, heart disease, diabetes or thyrotoxicosis.

(Advertisement)

patient has a cold, the coughing and sneezing will exaggerate this soreness. The diaphragmatic restriction caused by the enlarging uterus also makes breathing more difficult, particularly when the patient lies down. A cold compounds this difficulty.

Treating a cold in pregnancy requires two additional considerations. The patient should be told that the symptoms may last longer lest she become discouraged, and she should be reassured that the treatment will not damage the fetus. Although there are still some women who seem blissfully ignorant regarding matters of health (and these need to be cautioned not to take medication recommended by friends), most of our maternity patients are aware of the thalidomide tragedy. These women need constant reassurance that the symptoms of a cold can be treated, and that the medication is safe. Fortunately, many of the drugs which are of benefit have been in use long enough and widely enough so that such a statement can be offered. Occasionally one encounters a patient who is so anxious to avoid medication that she is extremely reluctant to take anything at all. Since cold is self-limited, it seems reasonable enough to give such a patient the choice and not to force drugs on her if she is obviously afraid of taking them.

The most distressing symptom of the common cold is the nasal congestion. This can be mitigated by the use of a decongestant which will help reduce the postnasal drip and the coughing caused by it. The kind of a cough which is described as a "tickling" in the throat and which is apt to occur when the patient goes to bed is usually due to nasopharyngeal congestion rather than inflammation in the lower respiratory tract.

There are many cough mixtures available. Most contain an antihistamine, a decongestant, and a cough "suppressant." Should cough suppression be desirable, it is important to remember not to use both a decongestant tablet and such a cough mixture as the patient would be getting a double dose of the decongestant. With some patients, the placebo effect of a cough syrup may be important and a liquid preparation might be substituted for an oral tablet.

For a sore throat, candy drops or lozenges at frequent intervals are soothing. It is not only unnecessary but unwise to use antibiotic lozenges or drops. The use of antibiotics in an uncomplicated cold is contraindicated and should be scrupulously avoided.

In summary, a cold in pregnancy is more severe and longer lasting. The treatment of the symptoms with local and systemic decongestants will make the patient more comfortable.

Apparently the cold is so common in pregnancy that it has received very little attention in the literature. References are almost non-existent and the few which are available add little to the common knowledge, are out-dated, or are not helpful. Thus the usual bibliography is not appended.



Relieve his sniffles, her concern, and about half your phone calls. Tell her to get "The Orange Medicine"



Triaminic® syrup

Each teaspoonful (5 ml.) contains:

Phenylpropanolamine hydrochloride	12.5 mg.
Pheniramine maleate	6.25 mg.
Pyrilamine maleate	6.25 mg.

For nasal congestion you can bring quick, lasting comfort to your little patients with Triaminic Syrup. You may occasionally encounter these side effects: drowsiness, blurred vision, cardiac palpitations, flushing, dizziness, nervousness or gastrointestinal upsets. Precautions: the possibility of drowsiness should be considered by patients engaged in mechanical operations requiring alertness. Use with caution in patients with hypertension, heart disease, diabetes, or thyrotoxicosis.

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Law and Medicine

Legal Immunity and Progress*

IN THE HIGHLY organized interdependent society of our time the three disciplines, medicine, law, theology, are more closely entwined than ever before. The medical breakthrough developed in the laboratory today may well become the standard by which the doctors' conduct is judged legally tomorrow. The life reclaimed tomorrow from the ravages of what is considered a terminal disease today presents theological and legal problems never before raised.

It has been generally true that society places the scientific advancement in a philosophical and legal perspective only after the potential consequences of the breakthrough are understood. However, today the *lawyer* and the *theologian* can no longer go about the leisurely development of their systems which have been historically valid. Since today's new clinical technique follows hard upon yesterday's laboratory discovery, the lawyer and the theologian must be ready to reinterpret their systems and revise their axioms to serve a society which *will* avail itself of new medical techniques whether the law and the church be ready or not.

The lawyer should attempt to constantly form, reform, assess, reassess, postulate and repostulate rules of practice and standards of conduct which will assist the profession as it moves ahead. The law, if it serves its function, will give the doctor a framework within which he may define the permissible limits of his new techniques and will also provide some type of reliable measuring device by which he can judge what is expected of him. If the law does this, then it has at least performed part of its function not only to the medical profession but to society in general.

As the medical profession moves into new areas of treatment and techniques, the legal institution must not go along merely as a wagging tail but must also serve as a guardian and conservator of the older principles which, if retained, will assist the inevitable progress of science. Indeed the law must continue to serve as a stabilizing device giving order and form to progress without impeding its advance.

Physician's Judgment

Foremost among the now accepted principles which must be jealously preserved is the immunity of the physician's judgment.

No Liability for Error in Judgment

Historically it has been the law that a doctor cannot be held for errors of judgment where there is a reasonable doubt as to the nature of the condition and the best method of treatment. A physician entitled to practice his profession, possessing the requisite qualifications, and applying his skill and judgment with due care, is not ordinarily liable for damages consequent upon an honest mistake or an error in diagnostic judgment, in prescribing a treatment or determining upon a certain operation. This principle must be retained. Medicine will continue to be as it has always been—an inexact science dealing with the most complex of mechanisms.

*Presented at the Annual Meeting of the Minnesota State Medical Association in Duluth, May 16, 1967.

Guarantee in Medicine Impedes Progress

A physician cannot guarantee results nor should that be expected of him. If the doctor is to become the guarantor of his treatment, if he is to be held legally responsible for a correct judgment on all occasions, then there will be no progress. The physician will never dare exercise that judgment which makes the practice of medicine the art that it is. Experimentation and innovation will be dead, and the healing art will stagnate in timidity and reserve. If the law allows this, it will surely have failed. Only when the doctor is free to exercise his best judgment can the new techniques become tomorrow's standard procedures and society become the benefactor of progress and discovery.

Failure to Cure

Together with the preservation of the free exercise of judgment, the law must not allow a failure to cure to become the foundation for a presumption of negligence. That is, the medical profession must not become burdened with the doctrine known in the law as *res ipsa loquitur,** where the physician is exercising his medical judgment with skill. As science advances and the miraculous recovery of today becomes the commonplace cure of tomorrow, there may be temptation to embrace this doctrine by those unaware of its implications. It is the law in this state, as well as in most states, that a person bringing action for the neglect of a physician to use the degree of care, diligence and skill required must prove such neglect. As the law now stands, no presumption of negligence arises from the fact that an operation or treatment does not result in a cure. In other words, success is not guaranteed and the lack thereof is not evidence of culpability. Negligence must not be presumed from results. Otherwise the doctor would work under a constant and intolerable threat of failure and would ply his art with only the most conservative and accepted tools and techniques. Because of the threat of one failure, one hundred successes might be denied. If the law forces medical science to work within such a straitjacket, it will again have failed in its obligation both to medicine and to society in general. Progress will cease, innovation and experimentation will wither and die.

Standard for the Region

If medical science is to continue to progress it is important that the physician continue to be judged by the standard of learning and skill possessed by the average number of his profession in good standing in his locality. This has historically been the standard by which the physician has been judged and it is the only workable standard.

The Country vs. the Metropolitan Doctor

The country doctor with his less extensive resources and facilities and with the myriad demands upon his time has never been held to the standard of the physician working in the metropolitan area close to the facilities of medical schools, blood banks and large urban hospitals. The general practitioner has never been held to the same standard in treating a fracture, as has an orthopedist. The reasons are obvious.

Still, with the increased urbanization that inevitably will come in the next few years, with the ever-developing systems of communication and transportation which dissolve the barriers of time and space, there may be a

*See Test Your Word Score Page 53.

temptation to alter the historic standard. The rural doctor who is only minutes away from the urban center may come to be expected to possess the same degree of skill and learning as his colleagues in the city. As most doctors move into metropolitan areas and specialize, there may be a temptation to adopt a common norm by which all will be judged—including those who choose to remain in rural areas and serve that segment of the population. If the country doctor is to be held to the same standard of skill as the practitioner on the university medical school staff, then surely he will never attempt to use the techniques which that urban practitioner has developed. It is only where the rural physician knows that he will not be judged by the urban standard that he will bring to his patients the advances that the urban specialist with his more extensive facilities has developed.

Free Choice of Physician

The patient has always had the right to refuse to follow a course of treatment and to terminate the doctor-patient relationship at any time. If new techniques and methods are to flourish the patient must be free to disregard his doctor's orders, to walk out of the hospital or the doctor's office, and to fire his physician without cause. With the inherent risks and hazards of such developing techniques as kidney transplantation, kidney dialysis machines and heart surgery, the right of the patient to refuse such treatment must be guarded. The real promise which medical advance holds will become apparent to a public which chooses of its own accord to accept the risks.

Accompanying the right of the patient to balk at progress must be an equal protective measure for the physician. Where a patient refuses to submit to the reasonable treatment prescribed, the onus must be on the patient and not on the doctor.

Comments

Such then are at least some of the traditional foundation stones which the law long ago placed beneath the practice of medicine, and they must remain if the institution of the law is to continue to assist the medical profession. Finally, however, both the lawyer and the doctor must share a common ideal if each is to lend his unique talents to the advancement of the healing science. Both must carry a fierce and dedicated commitment to the prolongation of life. The doctor must not hesitate or reject application of new methods and techniques that will assist in the prolongation of that life to which he has committed his talents. It is at this point then that the lawyer must demonstrate his commitment to the same ideal. For only the lawyer, using the techniques available to him, can urge upon society the legal protections and safeguards which will free the doctor to more vigorously pursue that goal to which he has dedicated his professional life. Confident that he is practicing his profession in a society in which the law recognizes that with progress come risks, and that with the exercise of judgment come failures, the doctor will more eagerly approach his task. If the lawyer has assisted in some small way in creating a legal framework within which the doctor can practice with confidence, then the lawyer goes where the doctor goes—toward future progress.

An English Court said in 1954: "We should be doing a disservice to the community if we imposed liability on hospitals and doctors for everything that happens to go wrong. Doctors would be led to think more of their own safety than of the good of their patients. Initiative would be stifled and

confidence shaken. A proper sense of proportion requires us to have regard for the conditions in which hospitals and doctors work. We must insist on due care for the patient, but we must not condemn as negligence that which is only misadventure."

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Pandora's Box

By the conquest of disease Europe and the world entered the bacteriological era. The pressure of disease was removed and its rods of chastisement broken. The ills that once flew out into the world from Pandora's Box were imprisoned once more and kept in safe custody.

Has man, with his conquest of disease, interfered without authorization in the cosmic plan? This question must be taken seriously. Were diseases designed to keep human propagation within bounds, to sweep away surplus populations and ensure living space in the world? If that be the case the balance has been upset by the conquest of disease. The Malthusian Law has proved its validity and the dangers prophesied are already looming on the horizon. Admittedly Europe could deport its huge population surplus to the new continents of America and Australia, but the peoples of Africa and Asia, who were also once condemned to a slow but certain death through epidemics, have been freed from the pressure of disease and have been awakened from their lethargy. Their vitality is increasing and they are shaking off the yoke of colonialism which brought them salvation from disease. Modern medicine applied to these people will, within a few generations—unless technology opens up new sources of life—render the earth uninhabitable. Asia alone in the year 2000 will number 2,000,000,000 and by its very mass will overshadow the people of Europe. The gift that Europe has given the world and the knowledge that has enabled it to overcome great dangers may possibly prove its own undoing.*

H. S. Glasscheib, M.D.: The March of Medicine, 1964.

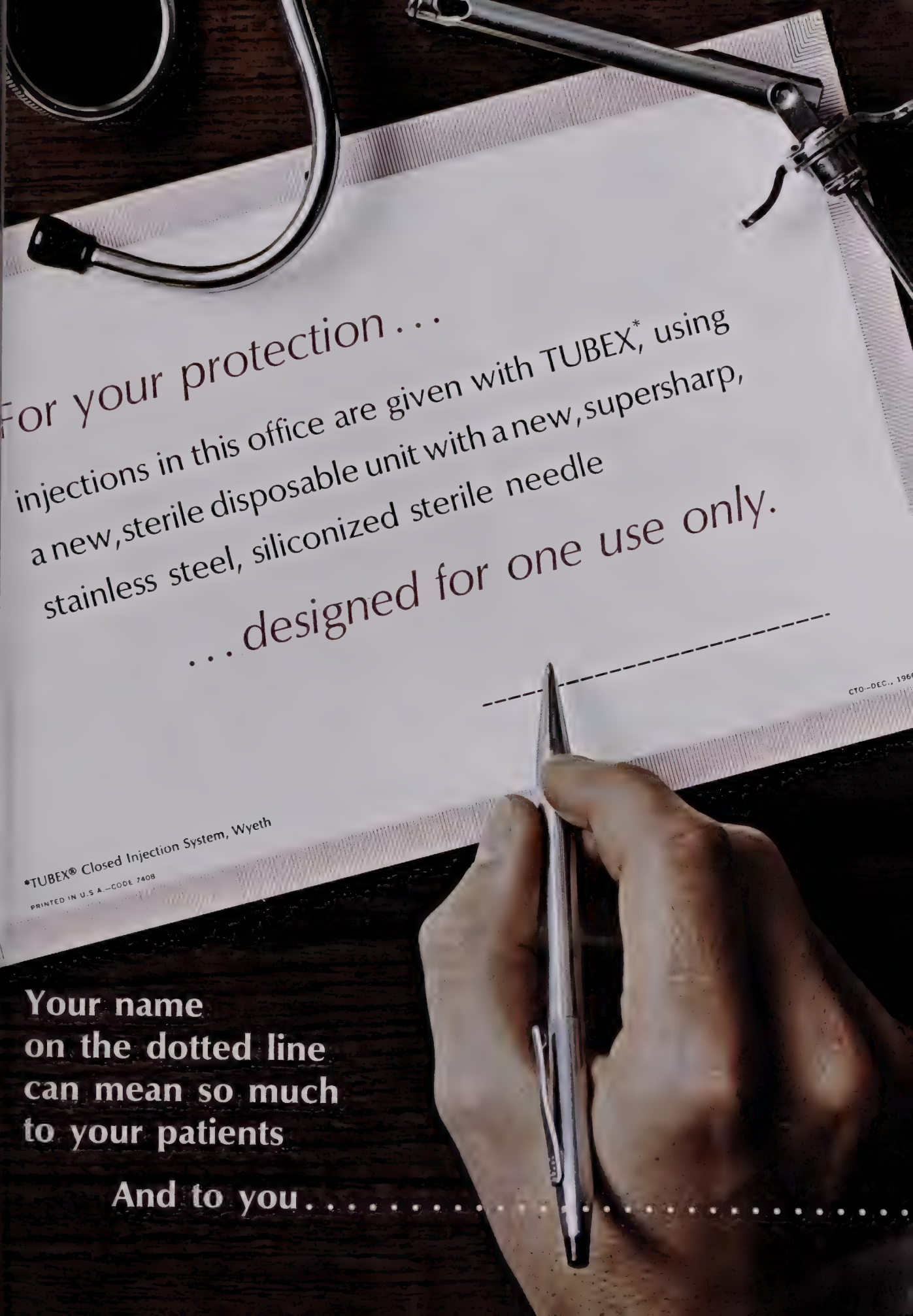
Medical Men on Postage Stamps

Hermann Boerhaave (1668-1738), Dutch physician and medical theorist and writer, is regarded as the first great clinical or 'bedside' teacher. He is reputed to have so raised the standards at the University of Leiden that students flocked to it from all over Europe. In 1938 The Netherlands commemorated his medical contributions by issuing a postage stamp in his honor.

William Harvey (1578-1657), English physician and anatomist who demonstrated that the arteries contained blood instead of air and originated the theory of the circulation of the blood, was honored by Russia on a special postage stamp issue in 1957.

Unfortunately there's a wide-spread view that the proper lubrication for a political machine is palm oil and not elbow grease.—Pure Oil News

The world of politics is always twenty years behind the world of thought—Chapman


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Grand Rounds

Transvenous Pacing of the Heart*

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Medical Resident

THE TECHNIQUE of transvenous pacing of the heart has become an important consideration in the management of patients with symptomatic heart block. Initially this technique was considered only in the temporary management of symptomatic A-V block associated either with Stokes-Adams syndrome or other complications. Although its short-term use remains as a primary indication, recent work has suggested catheter pacing for long-term therapy. This paper is designed to discuss the indications, technique, complications, and effects of transvenous catheter pacing and deals with the permanent implantable pacemaker only in passing. The paper also reviews the experience of transvenous pacing at Hennepin County General Hospital in ten patients.

In 1951 Callaghan and Bigelow[1] used a transvenous catheter electrode in dogs to maintain the heart rate by means of electrical pacing. The catheter was placed in the area of the sino-auricular node via the external jugular vein. In 1958, Furman and Robinson[2] described a method for catheter pacing in animals with experimentally produced heart block. Furman and Schwedel[3] reported the clinical use of transvenous pacing in two cases in the therapy for Stokes-Adams syndrome, using unipolar electrodes. Parsonnet and others[4] introduced the bipolar electrode catheter for clinical usage in patients with heart block. In the past five years, other investigators have reported the clinical usage of transvenous pacemakers.

It is generally accepted that the use of a transvenous pacemaker should be considered in high-grade or complete heart block in which a bradycardia or a ventricular arrhythmia leads to symptoms of the Stokes-Adams syndrome.

*Presented as a Medical Grand Rounds at Hennepin County General Hospital, March 21, 1967.

Etiology

Coronary Disease

The etiology of complete heart block is poorly understood. The primary cause was associated with coronary heart disease in a chronic form, or in association with hypertension or acute myocardial infarction (60 per cent).[5]

Hypertensive Disease

The other etiologic conditions included hypertensive heart disease, rheumatic cardiovascular disease, congenital heart disease, and others of unknown etiology. Friedberg points out that there is not always a correlation between the pathology of the conduction system in complete heart block and pathology found within coronary arteries. Coronary disease may not be a causative factor but rather a coexistent one.

Mechanical Stress

He feels an alternate theory is that prolonged mechanical stress with secondary fibrosis results in lesions within the conduction system resulting in complete heart block, a theory most applicable to chronic heart block. Carleton and others[6] include acute myocarditis as etiology of heart block, the probable cause in one of our cases at this hospital. Table 1 gives a more complete account of causes of heart block reported in the literature.

TABLE 1*
Etiology of Heart Block

	1956 Penton et al.		1956 Wright et al.		1958 Rowe & White		1963 Curd et al.		1963 Friedberg et al.
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.
Coronary heart disease	58	24	16	18	96	35	15	12	38
Coronary and hypertensive			10	11	68	24			10
Hypertensive	62	25	1	1			10	8	5
Rheumatic (H.D.)	21	8	3	3	23	8	13	10	6
Luetic			4	4					
Congenital			3	3	17	6	13	10	
Surgical							11	8	1
Diphtheric			2	2					
Miscellaneous	16	6	3	3	11	4	5	4	
Unknown	18	7			9	3	18	14	28
Ac. myo. infarction	49	19	9	10	38	14	33	25	12
Digitalis	27	11	31	34	16	6	12	9	
Uremia			8	9					
Total	251		90		278		130		100

*Friedberg, C. K., Donoso, E., Stein, W. G., Ann N Y Acad Sci 111:836, June, 1964.

Complications

No matter what the etiology may be, patients with complete heart block must depend upon the ability of the conduction system below the block to initiate ventricular impulses at a sufficient rate. A slow idioventricular rhythm associated with a complete A-V block may result in three clinical complications:[6]

1. The shift in or less frequent depolarization of the idioventricular pacemaker producing extreme bradycardia or complete asystole.
2. Repetitive episodes of ventricular tachycardia or ventricular fibrillation.

3. Intractable congestive heart failure.

Either of the first two complications may impair cerebral blood flow and produce the episodic syncopal-convulsive symptoms that characterize the Stokes-Adams syndrome.

Indications

The indications for use of a transvenous pacemaker may be divided into two categories, the short-term and the long-term usage.[7-29]

Short-Term Indications

Furman[8] summarized the short-term indications as follows: (1) Initial control of symptomatic heart block complicating acute myocardial infarction. (2) Control of heart block with complicating congestive heart failure. (3) Control of heart rate during surgery, including the implantation of a permanent pacemaker. (4) Control of heart rate during periods of permanent pacemaker failure. (5) Control in the patient who reverts to a conducted rhythm after a brief period of pacer therapy.

The patients in the last three categories experience Stokes-Adams symptoms at the time of their heart block; whereas the patients in the first two categories may or may not experience these symptoms. This paper will discuss the first category in more detail in view of its somewhat controversial nature.

The use of transvenous pacemakers in *acute myocardial infarction* with complicating complete heart block has proven to be an important adjunct to therapy[16-20,22,23,27]. Paulk and Hurst[23] pointed out in their study that with the advantage of recent electrical monitoring, our awareness of the incidence of complete heart block occurring in acute myocardial infarction has risen from 1.5% to 8%; their own incidence was 3.4%. The mortality has ranged from 40 to 100 per cent. Friedberg[5] points out that the heart block is almost always transient and disappears within seven to 14 days. Usually minimal lesions are seen in the conduction system at the time of autopsy, suggesting an ischemic or inflammatory etiology for the block. The transient nature of this block has led some investigators to believe that cardiac pacemakers are not indicated in this condition. In 14 of 18 patients reported by Courter and others[30] the heart block disappeared within six days. Jackson and Bashour[31] reported 27 of 32 patients reverting to a sinus rhythm by the fifth day. They pointed out that left heart failure was common but Stokes-Adams symptoms were uncommon in this type of heart block.

There still remain some patients in whom the use of a pacemaker may be indicated. Friedberg[5] considered three different types of *patients that may be predicted to have an unfavorable course* and in whom pacing may be needed. These included: (1) Patients with heart block and anterior myocardial infarction. (2) Patients with heart block and myocardial infarction whose electrocardiogram shows aberrant QRS complex. (3) Patients with associated Stokes-Adams attacks.

Cohen and others[32] reported a 75% mortality rate in 16 cases of anterior myocardial infarct with heart block as opposed to a 37% mortality rate in the inferior type of infarction with block. Since the right coronary artery (the supply to the A-V node in 90% of cases) is usually involved in an inferior infarct, associated heart block is due to ischemia and is transient. The block associated with an anterior infarct (involvement of the left coronary artery) is due to severe infarction of the septal muscle causing destruction within the conduction system. Cohen[32] pointed out that an aberrant QRS

complex suggested a pacemaker below the bifurcation of the Bundle of His. This type of complex was associated with an 80% mortality, while the patients with a QRS complex above the bifurcation showed a 48% mortality. Friedberg[5] postulates that a right coronary thrombosis (diaphragmatic-type infarct) will affect the A-V node; while the left coronary artery (anterior-type infarct) will affect the septum and damage both bundle branches, giving rise to an aberrant QRS complex from a lower idioventricular pacemaker. Varying results of pacing during acute infarction have been reported. Bruce and others[20] reported a reduction in mortality rate to 14% in seven patients. Paulk and Hurst[23] reported a series of 43 patients with heart block associated with myocardial infarction who had transvenous pacing. Seventy-five per cent of the patients had inferior infarctions, 7% had anterior, and 18% had both types. The overall mortality rate was 44%, thus remaining quite high. The degree of mortality was related to the severity of associated congestive heart failure. Similarly, the presence of shock or cardiac arrest was related to the mortality rate. The duration of active pacing ranged from one to twenty-one days in the survivors (56%). The authors feel that pacemaker insertion is not an innocuous procedure for a patient with a myocardial infarction. They prefer waiting until complete heart block intervenes. In 1,500 cases of myocardial infarction, these authors found the incidence of second degree heart block to be 8.7%, less than half of which continued into complete heart block. They also found that 25% of the survivors had a persistent complete heart block, a figure higher than previously reported. The authors attributed this to the survival of patients who would otherwise have succumbed from atrioventricular nodal infarction. It has also been pointed out that drugs such as digitalis or Pronestyl that might otherwise be contraindicated in heart block may be used in association with a transvenous pacemaker. It would appear that the role of a catheter pacemaker during acute myocardial infarction complicated by complete heart block becomes valuable provided its use is limited to certain clinical situations.

Transvenous pacing on a short-term basis not involving acute myocardial infarction is well reviewed by Yuceoglu and others.[7] The diagnosis of arteriosclerotic heart disease (non-acute) was made in 73 out of 78 patients studied. The various rhythm disturbances are summarized in Table 2. Immediate, satisfactory pacing was obtained in all but one patient. Duration of pacing was from one to fourteen days. This procedure was continued until optimal clinical improvement or before implantation of a permanent pacemaker.

TABLE 2*
Indications for Transvenous Pacemaker in 78 patients

	Number of cases
A-V block associated with Stokes-Adams syndrome:	
Ventricular standstill	30**
Ventricular tachyarrhythmia	27†
Ventricular standstill with ventricular tachyarrhythmia	6
Regular sinus rhythm with episodes of ventricular flutter-fibrillation unresponsive to Pronestyl or quinidine	1
Extreme regular sinus bradycardia with Stokes-Adams seizures due to cardiac standstill	1
A-V block with intractable congestive heart failure due to slow rate (low cardiac output)	12
Atrial fibrillation with extreme bradycardia, ischemic brain syndrome, and heart failure	1
Total	78

*Yuceoglu, Y. Z., Lunger, M., Dresdale, D. T.: Amer Heart J 71:6, 1966.

**Two with severe congestive heart failure, two with severe cerebral ischemia.

†One with severe congestive heart failure.

Long-Term Indications

With this procedure there are certain advantages, the primary one being the avoidance of a thoracotomy in the elderly patient who cannot tolerate such a surgical procedure. Long-term catheter pacing has also been recommended in the very young patient with congenital heart disease with block and in those patients who refuse a thoracotomy. Since December of 1963, Chardack and others[10] have treated 31 patients with a bipolar endocardial electrode catheter connected to an implanted pulse generator placed into the soft tissue below the clavicle.

Procedure

This paper deals primarily with techniques used at Hennepin County General Hospital. The externally placed pacemaker used has been a battery-powered pulse generator manufactured by Medtronic Inc., Minneapolis, Minnesota. Milliamperage as well as rate may be adjusted on the unit. The catheter used is a bipolar type with platinum terminals welded to stainless steel coils running in separate lumina within the catheter to the pulse generator. Stiffness and slight curvature are given to the catheter (needed for insertion and manipulation) by means of stainless steel stylets placed into the lumen of the coils. It is felt that the bipolar type of catheter electrode is superior to the unipolar type[4,11,15,33] which required an indifferent electrode placed in the subcutaneous skin of the chest wall. Patients complained of pain in this area during pacing. Furthermore, it was found that the bipolar electrode catheter was easier to position and did not require the degree of myocardial contact needed in the unipolar type.[33] The need for anticoagulants was abandoned with the use of the bipolar type, and the incidence of infection was lower.[11]

An outline of the general technique recommended is as follows:

1. The patient is placed in a recumbent position with the head turned to the left or right and the shoulder elevated.
2. The root of the neck is prepared and the external jugular vein is exposed.
3. An electrocardiogram monitor is present.
4. An external pacemaker should be available, preferably strapped to the chest.
5. A cut-down is performed upon the right external jugular vein with ligation of the proximal portion.
6. The catheter is inserted under sterile conditions and directed under fluoroscopy into the apex of the right ventricle.
7. If the patient's condition permits, various positions and respiratory efforts are tried.
8. Voltage usually necessary to pace is less than one milliampere, and a one-to-one ventricular response is a check upon proper placement. As a margin of safety the voltage is generally increased to 1.5 to 2.5 milliamps.
9. The pacing rate most often used is 70 impulses per minute but may be increased to capture from and suppress all ectopic foci.
10. The catheter is sutured into place at the cut-down site and sterile dressings are applied.

Because of freedom of movement of the patient and less chance for displacement, the external jugulars are preferred. The internal jugular veins as well as the arm veins can also be used for placement. In patients who will

likely need permanent transvenous pacing, the right external jugular vein should be spared at the time of initial catheter placement for interim pacing. The success of transvenous pacing depends upon the proper placement of the electrode tip within the trabeculae at the apex of the right ventricle. When the desired position is obtained, the stylets are withdrawn to assure flexibility of the catheter. Within weeks, the catheter becomes covered by a continuous layer of fibrous tissue. Improperly placed catheters lead to pacemaker failures. Unstable positions of the catheter tip include: (1) Close proximity to the tricuspid valve with advancement into right atrium. (2) High position in the pulmonary outflow tract. (3) Loops or tension within the catheter.

If a great deal of manipulation of the catheter is required, prophylactic antibiotics may be considered. Various techniques are described for permanent placement of transvenous pacemakers but, in general, the endocardiac electrode is of the bipolar type and the pulse generator is smaller and implanted within the subcutaneous tissue under local anesthesia.[40]

Complications

Arrhythmias

In a study of 96 insertions in 78 patients[7] the most common catheter complication was the occurrence of arrhythmias during insertion. Other complications are listed in Table 3.

TABLE 3*
Electrode Catheter Complications

Arrhythmias during insertion:	
Ventricular tachyarrhythmia requiring defibrillation	19**
Ventricular standstill requiring external pacing	6
Perforation of right ventricular outflow tract	2
Possible perforation of great cardiac vein	1
Repositionings (11 patients)	19
Bleeding	2
Thrombophlebitis	1
Infection	
Local, at phlebotomy site (saphenous)	2
Sepsis	2
Ulcerative bacterial endocarditis (rheumatic heart disease)	1
Death during catheter insertion	4

*Yuceoglu, Y. Z., Lunger, M., and Dresdale, D. T.: Amer Heart J 71:9, Jan. 1966.
**Total of 9 patients: 4 times in one patient, and 8 times in another. Both patients survived.

Perforation

Perforation of the right ventricle has occurred less frequently with the recommendation to remove the stylets after placement of the catheter. In Table 4 Chardack and others[10] report 16% of the cases complicated by either perforation or disruption of the coils probably due to the retained stylets. Fort[34] reported two cases of perforation of the right ventricle in patients who suffered no ill effects. Retrospectively, the clues to perforation were difficulty of pacing and the presence of a systolic sound along the left sternal border. Moss and Rivers[35] point out the roentgenographic demonstration of change in position as a helpful aid in discovery. Nathan and others[37] reported a 20% occurrence of this complication. Although there appear to be a few deaths reported from this complication, some authors[13] feel that it necessitates the placement of the catheter in the outflow tract rather than the ventricular apex. It is felt that foreshortening of the apex-base distance during systole

requires a catheter to be sufficiently compliant laterally as well as longitudinally. Thrombotic attachment to the endocardium limits this compliance. In one of our cases at this hospital, perforation of the septum occurred secondarily to remanipulation of the catheter.

Malposition

Malposition within the ventricle requiring repositioning occurred in about 14% of the patients reported by Yuceoglu and others.[7] This is usually due to inadequate initial placement, loosening of the subcutaneous stay sutures or placement of catheter within the arm. Besides malposition of catheter, pacemaker failure may occur on the basis of electrical failure (battery or catheter), dominant spontaneous rhythm, and loss of myocardial reactivity. Gordon[28] presents an organized regimen to locate the source of difficulty, using cavity lead electrocardiogram patterns as well as roentgenographic procedures.

Infections

Infections did not seem to be a significant complication of transvenous pacing.[24,11] Isolated cases of bacterial endocarditis[7] have been reported, as in one of our cases. Schwedel and Escher[11] pointed out the increased incidence of infection occurring in those patients who undergo repositioning and excess manipulation of the catheter. In these cases it is best to remove the catheter and replace it with another. Local infections at the catheter site occurred in 33% of the cases reported by Furman and others.[8]

Thrombophlebitis or complicating thromboembolic phenomena did not occur with any significance, and there was no advantage in anticoagulant therapy.

Many authors report the dangers of ventricular fibrillation occurring with transvenous pacemaking. This arrhythmia occurs secondarily to the pacemaker stimulus falling within the vulnerable period following the preceding conducted or ectopic ventricular depolarization. Chardack and others[10] showed that a stimulus of the magnitude of 40 to 45 ma. is needed to produce such an arrhythmia in the vulnerable period. This represents a 10 to 20-fold greater stimulus than the pacer produces. There still exists the danger of a competitive rhythm occurring with pacemakers and the chance of a much greater stimulus such as a P wave occurring in the vulnerable period. It is this consideration that gave rise to the demand pacemaker.[36,38] In demand pacing, the delivery of an electrical impulse is coupled to the preceding QRS complex, and delivery of a pacer impulse takes place only when a preset time interval after ventricular depolarization has been exceeded. In other words, the pacemaker paces when the spontaneous rate is lower than the preset pacemaker rate. Demand pacing avoids unnecessary continuous stimulation of the myocardium.

Effects of Pacing

Hemodynamics

It is generally felt that electrical pacing gives immediate favorable results. The hemodynamics of the heart are improved with pacing. Escher and others[12] studied 27 patients with complete heart block with respect to hemodynamics while being artificially paced. None of the patients were in congestive failure. All showed reduced cardiac output at their slow idioventricular rates, but there was a marked difference in cardiac output from patient to patient. In about one third of the patients, a normal cardiac output was achieved, indicating the significance of heart rate alone.

Optimal Fixed Rate

The optimal fixed rate for maximum comfort appeared in the 70's. This correlated with the level at which most reached their greatest percentage of increase in cardiac output. These patients were able to tolerate increased rates to suppress ectopic beats. The inability to increase cardiac output with exercise is a limiting factor in fixed artificial pacemaking. It may be said that a normal cardiac output may be maintained by a healthy myocardium through a compensatory increase in stroke volume during heart block. A diseased myocardium may be incapable of showing this compensation such that changes in cardiac output are completely dependent on heart rate.

Many investigators have reported the use of drugs in the treatment of complete heart block, a subject beyond the scope of this paper.[41-43] Certainly such drugs as isoproterenol, epinephrine, steroids, chlorothiazides have their places in the overall treatment of complete heart block. There still remain the patients that are not responsive to drug therapy or develop the undesirable effects of these drugs. There are also the patients that have associated complications that need immediate resolution in which transvenous pacemaking may be life-saving. Karlson and others[21] report that in 47 patients with heart block and Stokes-Adams syndrome treated medically with isoproterenol, 70% continued to have Stokes-Adams seizures, 20% showed ventricular arrhythmias and 10% showed a good response. Chardack and others[10] compared the survival of 50 pacemaker patients on whom a two-year followup was available with comparable patients treated by drugs alone. With the exception of a 10% mortality rate associated with surgery, the per-cent survival after one and two years was significantly higher in the paced group of patients.

Our Results as of March, 1967

Our experience with transvenous pacemakers in 10 patients is summarized in Table 4. Twelve insertions were made in 10 patients, all of whom had complete heart block. The etiology in 5/10 was probably arteriosclerotic heart disease; 4/10 acute myocardial infarction; and 1/10 probable myocarditis. All were paced on a short-term basis ranging from one hour to 13 days.

Complications

Complications of pacing included: (1) 4/12 insertions: difficulty with technique. (2) 1/12 insertions: infection and septicemia. (3) 1/12 insertions: perforation of septum. (4) 7/12 insertions: poor pacing.

Mortality

The results showed that 3/10 patients recovered with a loss of the complete block; 5/10 patients went on to have a permanent pacer; 2/10 patients died, both from acute myocardial infarcts.

Summary

Transvenous pacemaking should be an important consideration in the treatment of symptomatic heart block. Its primary indication has been in the presence of complete heart block with Stokes-Adams symptoms or other resulting complications such as refractory congestive heart failure.

TABLE 4

Name	Age	Sex	Indications	Days Paced	Pacer In place	Complications	Results
M.B.	53	M	Inferior M.I. with complete heart block; poor response to Isuprel.	6	11	Difficulty rt. jug. vein; local infection cutdown site; unable to remove catheter.	Spontaneous resolution; 2° to 1° block in 7 days.
R.B.	64	M	Anemia; 2° heart block with RBBB; documented episodes of asystole –3°.	8 48	8 48	Complete asynchrony 2° to poor catheter placement. Infection cutdown site that advanced to septicemia and bacterial endocarditis; perforation of septum; 2nd catheter placed.	Permanent pacemaker.
A.M.	74	M	ASHD; old ant. M.I.; Acute inf. M.I.; RBBB-AV dissociation.	1 hr.	10 hrs.	Unable to locate rt. jug.—rt. arm vein.	Died within 24 hrs.
C.H.	20	M	URI for 7 days; Stokes-Adams attack –3° heart block, pulse –30; no response to Isuprel; viral myocarditis.	6	10	Poor pacing—required remanipulation.	Spontaneous recovery.
J.L.	79	M	Stokes-Adams syndrome—complete 3° block. Pulse 44/min.	13	13	Rt. jug. unsuccessful—left jug.; Completion with sinus pacer.	Permanent pacer.
B.B.	80	M	Stokes-Adams syndrome; Pulse 36/min.	5	5	None.	Permanent pacer.
C.L.	61	M	ASHD; Acute inf. M.I. 1° block –3° block on day 3; poor resp. to Isuprel; CHF.	1½	7	Asynchrony.	1° block on day 5; Transferred after 18 days.
C.S.	74	M	Stokes-Adams syndrome; Isuprel ineffective; poor sensorium.	9	14	Sinus pacemaker completion left cephalic vein.	No change in sensorium. Discharged 2:1 block.
			Stokes-Adams syndrome	4	4	Unsuccessful l. jug. l. brachial; Missed beats.	Permanent. Died 3½ mo.
L.B.	62	M	Auto trauma; acute inf. M.I.; Stokes-Adams symptoms with 3° block; Intractable CHF.	0	8	Catheter in pulm. outflow tract—never paced.	Died. Post: Rt. coronary occlusion.
A.P.	74	F	Stokes-Adams with 3° block.	8	8	Difficulty pacing.	Permanent.

Short-term pacing entails control of heart rate during an acute myocardial infarct, acute congestive failure, preparation for/or during surgery, permanent pacemaker failure, or periodic rhythm disturbance. The use of pacing in acute myocardial infarction is controversial. The known incidence of complete heart block in acute myocardial infarction is increasing and the mortality remains quite high.

Long-term transvenous pacing has been used in the patient who cannot tolerate a thoracotomy.

Primary complications have included arrhythmias during insertion, perforation, malposition, pacemaker failure and infection. The danger of ventricular arrhythmias, primarily fibrillation, has increased interest in demand pacemaking. Generally there is improved hemodynamics with pacemaking. Overall evaluation shows pacing to be superior to drug management in complete heart block.

Transvenous electrical pacing of the heart is a relatively safe, effective, reliable, and oftentimes life-saving measure for immediate as well as for long-term control of symptomatic heart block.

Case Report

A 74-year-old white female with a six to seven-year history of hypertension suffered some syncopal episodes during the week prior to admission, causing some minor head trauma. The patient was admitted after loss of consciousness while driving her car. Her pulse on admission was 40 and her blood pressure 150/80. Documentation of episodic, symptomatic ventricular fibrillation associated with complete heart block was obtained on electrocardiogram. A transvenous pacemaker was inserted through the right external jugular vein 24 hours following admission. The patient was paced at 60 to 70 beats per minute at 1.5 to 2 milliamps, with definite subjective improvement. On the fourth hospital day of pacing she failed to pace periodically, the failure seemingly related to change in position, and she was having multiple premature ventricular contractions during asynchrony. A gradual increase to 10 milliamps was required for pacing by the eighth day. On the ninth hospital day a permanent epicardial pacemaker was implanted. The patient did well following surgery and was discharged on the twenty-sixth hospital day.

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13-43 May be secured from the Grand Rounds Editor.

Thirty-First Annual Meeting

The New Orleans Graduate Medical Assembly

The thirty-first annual meeting of The New Orleans Graduate Medical Assembly will be held March 4, 5, 6, 7, 1968, headquarters at The Roosevelt Hotel.

Nineteen outstanding guest speakers will participate and their presentations will be of interest to both specialists and general practitioners. The program will include fifty-one informative discussions on many topics of current medical interest, in addition to a clinicopathologic conference, symposia, medical motion pictures, round-table luncheons, and technical exhibits. This program is acceptable for thirty-two (32) elective hours by the American Academy of General Practice.

An interesting and enjoyable program of entertainment for visiting ladies has been planned.

Of special interest will be a one-day pre-Assembly symposium scheduled for Sunday, March 3, on "Sexual Problems in Clinical Practice." Six papers, together with a panel discussion, will be presented by six authorities on this subject.



Abstracts, Briefs and Commentaries

SQUAMOUS CELL CARCINOMA OF THE PYRIFORM SINUS

During a twenty-year period, 1940-1960, 119 patients completed the recommended treatment for squamous cell carcinoma of the pyriform sinus. The patients were on one of the head and neck services of the Roswell Park Memorial Institute.

Sixty-six patients were treated by radiation alone during the first 16 years. No surgery was done for this type of lesion during that period. The five-year survival was 3%. When broken down into three periods of time to eliminate possible differences in irradiation technique the survival rate remained the same.

Fifty-three patients were diagnosed and treated from 1954 to 1961, twenty-six of them by radical surgery consisting of total laryngectomy, partial pharyngectomy, and radical neck dissection. The five-year survival in this group was 20%. Metastatic disease was found histologically in 82% of patients treated by radical surgery.

Harrison H. Farley, M.D.
Minneapolis, Minnesota

Marchetta, Frank C., Sako, Kumas, Holyoke, E. Douglas: Squamous Cell Carcinoma of the Pyriform Sinus. Amer J Surg 114:4:507, 1967.

THE COMMUNITY-UNIVERSITY HEALTH CARE CLINIC

The Community-University Health Care Clinic initiated in July, 1966, as a University Community Program is a pilot project within a larger Children and Youth project administered by the Minneapolis Health Department.

Situated in an urban area unusually needful of a wide range of health care, the primary goal of this program of comprehensive social, physical and mental health care is education of resident physicians, medical and dental students and students of the allied health disciplines. Collecting data for research in associated urban problems is a vital secondary goal.

The project aims to provide care to eligible children from birth through high school in an area defined by the geographical confines of Seward, Adams, and Greeley Elementary School Districts in South Minneapolis. Of

the 7,200 children within the area approximately 2,900 have been defined as eligible because of low family income. A preliminary survey carried out in the summer of 1966 revealed that 94% of the area children under five years of age had never seen a dentist, 53% of the whole 7,200 had never been treated by a private physician and only 9% had received care at the Hennepin County General Hospital.

A high incidence of psycho-social, speech, language and auditory disability accents the need for preventive measures, as well as long-term care, involving the project staff, citizens' groups and schools.

A clinic building converted from an apartment house near the geographical center of the area opened in February, 1967. A substation staffed by public health nurses from the Minneapolis Health Department occupies the fourth floor. The staff is on call during non-office hours for the patients enrolled, with hospitalization when necessary at one of the adjacent cooperating community hospitals.

The patient population currently under care has grown mainly from neighbor or self-referral, with some referral from the cooperating public health nurses.

The recent formation of a University Hennepin County Medical Society liaison committee to work with the project staff will do much to further develop common interests in the promotion of suitable training opportunities for professionals desiring a career in clinical practice.

Edward C. Defoe, M.D.
Minneapolis, Minnesota

METHODS OF BIRTH CONTROL*

Birth control is an accepted technique of preventive medicine—its simple goal: every pregnancy wanted and planned. Physicians should be equipped to be competent advisors concerning the effects of age, parity, and pregnancy interval on pregnancy outcome, as well as effective and safe methods of birth control.

If the couple is young, the physician may counsel postponement of pregnancy until one or both partners have completed their educations. He may also advise contraception if his experience leads him to believe that adjustment is virtually always necessary in early marriage and that it can be better made by the couple before than during a pregnancy.

The best allies of successful pregnancy are youth, normal germ plasm, sound health, and good medical care. The optimum years for childbearing are ages 20 to 30 for the mother. After the father is 45 both stillbirth and congenital malformation rates rise. Beyond the fourth child maternal and perinatal mortality rates rise slowly through para six, moderately through para eight and relatively rapidly thereafter. The best pregnancy interval from the viewpoint of infant survival is two to three years between the end of one pregnancy and the beginning of the next. The physician knowing the health of the woman should advise against further pregnancies, if in his judgement medical contraindications exist.

Contraception is a rapidly developing field and the physician must be

*Presented at the Minnesota State Medical Association Annual Meeting, Duluth, Minnesota, May 16, 1967.

sufficiently conversant with it so that he may offer the individual couple several methods of birth control from which to choose. No single method is satisfactory for all couples under all conditions and circumstances. The doctor should frankly inquire into the sexual adjustment of couples under his care, and if he thinks their method of contraception contributes to lack of sexual satisfaction in either husband or wife, he should advise the trial of a different technique.

The author classifies contraceptive techniques in six categories on the basis of effectiveness when used correctly:

Class I — Gestagens by mouth or injection
Class II — Intrauterine device, condom, diaphragm and cervical cap
Class III— Aerated intravaginal foam, rhythm when practiced with the aid of basal body temperature
Class IV—Ordinary intravaginal chemical, jellies, creams, tablets, suppositories
Class V — Coitus interruptus, rhythm when practiced by calendar
Class VI— Post-coital douche

Since there is such latitude of choice among the first three classes, it seems pointless for the physician to recommend methods listed in categories IV, V, and VI.

The advantages, disadvantages and safety of the various methods listed in the first three categories will be discussed.

Alan F. Guttmacher, M.D.*
New York, New York

*President, Planned Parenthood Federation of America, Inc.

DAMAGES UPHELD

Damages for 1.5 million dollars were awarded a woman in Miami, Florida, against two physicians and a hospital. She was paralyzed from the neck down following an operation for varicose veins and hemorrhoids. The type of anesthesia was not stated. The award was made by a Circuit Court Judge.

Note: How many physicians or clinics could survive such a judgment even with unusual help from their insurance coverage?

Stanley R. Maxeiner, Sr., M.D.
Minneapolis, Minnesota

AMA NEWS May 22, 1967.

Patriotism

When you call me Red—add white and blue.—Don Iddon, London Daily Mail

Life is an earnest business, and no man was ever made great or good by a diet of broad grins.—J. S. Blackie

The mule is half horse and half jackass, and then comes to a full stop, nature discovering her mistake.—Josh Billings



WHAT DOES GALVANIC SKIN RESISTANCE DEMONSTRATE ABOUT THE EFFECT OF VALIUM (diazepam)?

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This gives a graphic representation of changes which the body may undergo in reacting to stress. The application of modern statistical analysis to these graphs provides a yardstick by which the calming effect of Valium (diazepam) can be measured quantitatively.

Before prescribing, please consult complete product information, a summary of which follows:

Contraindications: Infants, patients with a history of convulsive disorders, glaucoma or known hypersensitivity to drug.

Warning: Not of value in the treatment of psychotic patients, and should not be employed in lieu of appropriate treatment.

Precautions: Limit dosage to smallest effective amount in elderly or debilitated patients (not more than 1 mg, one or two times daily initially) to preclude ataxia or oversedation, increasing gradually as needed or tolerated. As is true of all CNS-acting drugs, until correct maintenance dosage is established, advise patients against possibly hazardous procedures requiring complete mental alertness or physical coordination. Driving during therapy not recommended. In general, concurrent use with other psychotropic agents is not recommended. If such combination therapy is used, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam), such as phenothiazines, barbiturates, MAO inhibitors and other antidepressants. Advise patients against simultaneous ingestion of alcohol or other CNS depressants. Safe use in pregnancy not established. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Observe usual precautions in impaired renal or hepatic function. Periodic blood counts and liver function tests advisable in long-term use. Cease therapy gradually.

Side Effects: Side effects (usually dose-related) are fatigue, drowsiness and ataxia. Also reported: mild nausea, dizziness, blurred vision, diplopia, headache, incontinence, slurred speech, tremor and skin rash; paradoxical reactions (excitement, depression, stimulation, sleep disturbances, acute hyperexcited states, hallucinations); changes in EEG patterns during and after drug treatment. Abrupt cessation after prolonged overdosage may produce withdrawal symptoms (convulsions, tremor, abdominal and muscle cramps, vomiting, sweating) similar to those seen with barbiturates, meprobamate and chlordiazepoxide HCl.

Dosage—*Adults:* Mild to moderate psychoneurotic reactions, 2 to 5 mg b.i.d. or t.i.d.; severe psychoneurotic reactions, 5 to 10 mg t.i.d. or q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; muscle spasm with cerebral palsy or athetosis, 2 to 10 mg t.i.d. or q.i.d. *Geriatric patients:* 1 or 2 mg/day initially, increase gradually as needed and tolerated. (See *Precautions.*)

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg; bottles of 50 and 500.

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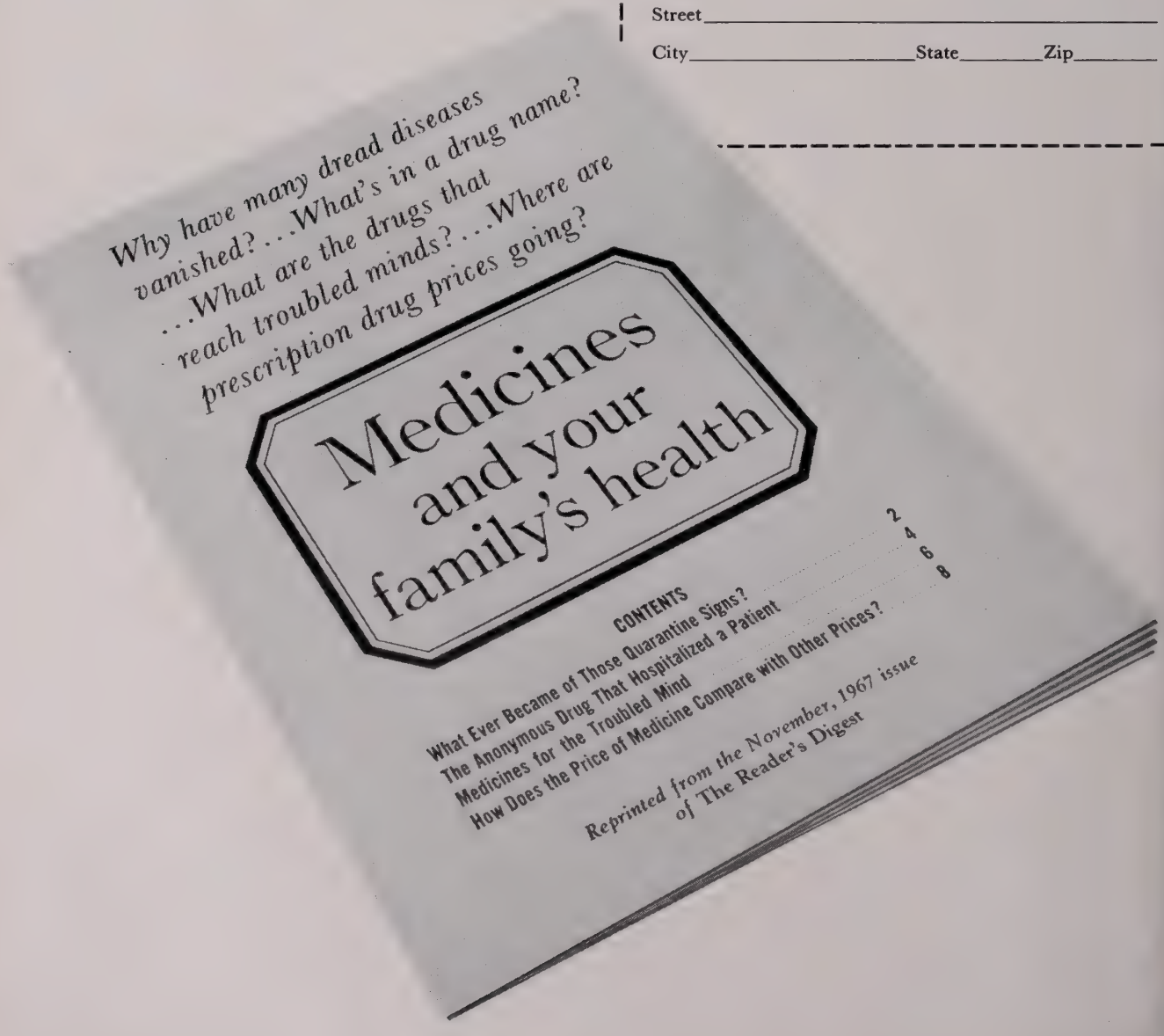
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Book Reviews

Books are a guide in youth, and an entertainment for age. They support us under solitude, and keep us from becoming a burden to ourselves. They help us to forget the crossness of men and things, compose our cares and our passions, and lay our disappointments asleep. When we are weary of the living, we may repair to the dead, who have nothing of peevishness, pride, or design in their conversation.—Jeremy Collier

ATLAS OF VASCULAR SURGERY—Hershey and Calman. Second Edition, Published February 1967. C. V. Mosby Company, St. Louis.

This Atlas of Vascular Surgery is a very fine survey of the subject. It contains 307 pages of text with a useful 10-page index. The illustrations are excellent drawings that are easily understood.

Short and clearly descriptive text material is sufficiently complete to describe the various procedures. This Second and Revised Edition is up to date in the modern advancements of this rapidly changing field of surgery.

Chapters include Methods of Diagnosis, Aneurysm Disease, Occlusive Disease, Embolic Problems and Vascular Injuries.

Special areas involve descriptions of Superior Mesenteric Artery Problems, Renal Vascular Hypertension, Cerebral Occlusive Disorders, and Portal Hypertension. The value and methods of sympathectomy are related. Venous problems are outlined, including acute thrombosis and chronic venous disease.

Finally, another portion covers various amputations as related to the vascular problems.

The reviewer has found this Atlas to be most instructive. He can recommend this book as a useful reference source for the student, the resident, and the practicing surgeon.

J. H. Strickler, M.D.
Minneapolis, Minnesota

HANDBOOK OF ORTHOPEDIC SURGERY—Shands & Raney. C. V. Mosby Co., St. Louis, Publisher. Pages: 572. Illustrations: 269. Price: $12.00.

A handbook on orthopedic surgery obviously cannot cover in detail the entire scope of all the orthopedic problems, though it can give valuable information to the physician, whether in general practice, or in one of the specialties, who wishes to use it for reference material.

On this basis Shands and Raney have prepared a brief but comprehensive review of a great variety of orthopedic problems that can be encountered in a large general practice.

It is interesting to observe that the cervical root syndrome is accorded its relative significance and is not over-emphasized by the use of the jury-appealing term of whiplash.

The bibliography is interestingly arranged in a manner in which a curious investigator can obtain ready reference to a variety of items that might interest him. The book is well bound.

Carl O. Rice, M.D.
Minneapolis, Minnesota

ATLAS OF INTESTINAL STOMAS — Turnbull & Weakley. Publisher: C. V. Mosby Company. Price: $21.50.

This monograph on intestinal stomas has been beautifully prepared with numerous illustrations depicting the details of technique.

The intestinal stomas are designed principally in the operative treatment of ulcerative colitis and carcinoma of the colon, where it is necessary to make a permanent or a temporary deviating stoma.

To the surgeon who does this type of operation this monograph should be available, as it details a considerable number of procedures that have been found to be of value in the unusual circumstance.

Carl O. Rice, M.D.
Minneapolis, Minnesota

FOOT DISORDERS — MEDICAL AND SURGICAL MANAGEMENT — Nicholas J. Giannestras, M.D. Fleansebiger 1967. Price: $22.00.

In compiling a book with regard to foot disorders the author has commandeered the talents of a dozen outstanding men who have had interest in the various phases of foot disorders.

As specialties and sub-specialties develop, it is readily understandable that foot disorders could become one of the important sub-specialties of orthopedic surgery. In addition to orthopedic problems, there are also many medical problems as indicated in the chapter dealing with rheumatoid foot and neurologic diseases of the feet, gout and allied disorders. This book is well written, well edited and advantageously illustrated.

Carl O. Rice, M.D.
Minneapolis, Minnesota



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Precautions: Use with caution in patients hypersensitive to sympathomimetic compounds, who have coronary or cardiovascular disease, or are severely hypertensive.

Dextro-amphetamine sulfate: Excessive use by unstable individuals may result in psychological dependence.

Meprobamate: Careful supervision of dose and amounts prescribed is advised, especially for patients with known propensity for taking excessive quantities of drugs. Excessive and prolonged use in susceptible persons, e.g. alcoholics, former addicts, and other severe psychoneurotics, has been reported to result in dependence on the drug. Where excessive dosage has continued for weeks or months, reduce dosage gradually. Sudden withdrawal may precipitate recurrence of preexisting symptoms such as anxiety, anorexia, or insomnia; or withdrawal reactions such as vomiting, ataxia, tremors, muscle twitching and, rarely, epileptiform seizures. Should meprobamate cause drowsiness or visual disturbances, reduce dosage and avoid operation of motor vehicles, machinery or other activity requiring alertness. Effects of excessive alcohol consumption may be increased by meprobamate. Appropriate caution is recommended with patients prone to excessive drinking. In patients prone to both petit and grand mal epilepsy meprobamate may precipitate grand mal attacks. Prescribe cautiously and in small quantities to patients with suicidal tendencies.
Side Effects: Overstimulation of the central nervous system, jitteriness and insomnia or drowsiness. Dextro-amphetamine sulfate: Insomnia, excitability, and increased motor activity are common and ordinarily mild side effects. Confusion, anxiety, aggressiveness, increased libido, and hallucinations have also been observed, especially in mentally ill patients. Rebound fatigue and depression may follow central stimulation. Other effects may include dry mouth, anorexia, nausea, vomiting, diarrhea, and increased cardiovascular reactivity.

Meprobamate: Drowsiness may occur and can be associated with ataxia; the symptom can usually be controlled by decreasing the dose, or by concomitant administration of central stimulants. Allergic or idiosyncratic reactions: maculopapular rash, acute nonthrombocytopenic purpura with petechiae, ecchymoses, peripheral edema and fever, transient leukopenia. A case of fatal bullous dermatitis, following administration of meprobamate and prednisolone, has been reported. Hypersensitivity has produced fever, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, stomatitis, proctitis (1 case), anaphylaxis, agranulocytosis and thrombocytopenic purpura, and a fatal instance of aplastic anemia, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity, usually after excessive dosage. Impairment of visual accommodation. Massive overdosage may produce drowsiness, lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse.

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Continued to Page 160.

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Average Adult Daily Dosage: 150 mg q.i.d. or 300 mg b.i.d. Should be given 1 hour before or 2 hours after meals, since absorption is impaired by the concomitant administration of high calcium content drugs, foods and some dairy products. Treatment of streptococcal infections should continue for 10 days, even though symptoms have subsided.

In the treatment of syphilis a dosage schedule of a total of 12 to 18 Gm. given in equally divided doses over a period of 10 to 15 days should be followed. Close follow-up observation of the patient is recommended, including appropriate laboratory tests, since demethylchlortetracycline has not had adequate evaluation in all stages of syphilis. Spinal fluid examination should be included as part of this follow-up.

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Special Article

Cystic Fibrosis Detection Clinic Program in Minnesota*

WARREN J. WARWICK, M.D.**
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Minneapolis, Minnesota

In 1965 we began planning a large scale sweat test screening program for cystic fibrosis in school children. The decision to do this program was based on four observations: (1) cystic fibrosis is estimated to occur in one of every one to two thousand newborn infants;[1] (2) nation-wide statistics indicate that one third of the deaths from cystic fibrosis occur by one year of age and one half by four years;[2] (3) the mortality rate for children with cystic fibrosis receiving prophylactic pulmonary cleansing therapy may be less than one seventh that of the national average;[3] (4) our attempts to find children with cystic fibrosis in Minnesota indicated that four out of five children born with the disease (assuming a newborn incidence of one in 1000) may not have been diagnosed.[4] Our purpose was to find the prevalence of undiagnosed children in order to check our estimates of the incidence and mortality and to give any undiagnosed children found the benefits of improved methods of treatment.[5] We selected the heat stimulus-chloride ion electrode sweat test for this survey because it is accurate, fast, and inexpensive when compared with the usual sweat tests.[6]

Testing Plan

Community Selection

Twenty-six cities and towns throughout Minnesota were included in this screening program. Because of the expenses involved, financial support was a major factor in community selection. The program was sponsored by the Minnesota Chapter of the National Cystic Fibrosis Research Foundation with financial and direct assistance from the Minnesota Mrs. Jaycees. Clinics were scheduled in selected

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communities throughout the State of Minnesota in which the local Mrs. Jaycees' organization was able to provide financial assistance and volunteers for the project.

Organization of the Testing Program

The Minnesota Chapter of the National Cystic Fibrosis Research Foundation and the Minnesota Mrs. Jaycees obtained the cooperation of physicians and school officials in each of the 26 selected communities. The local news media were used whenever possible to provide lay education concerning cystic fibrosis and the "Cystic Fibrosis Detection Clinics."

The Cystic Fibrosis Care, Research, and Teaching Center at the University of Minnesota provided two technicians and the necessary equipment.

Form letters containing permission slips were distributed to children in kindergarten and grades one through four to be sent home to parents several days prior to the scheduled test day or days.

The Sweat Test

Whenever possible the screening tests were conducted in large, well ventilated rooms, usually gymnasiums, in local schools. Two sturdy tables were set up parallel to each other, about four feet apart at one end of the room and near electrical outlets.

After the equipment was set up and standardized[6] and the eight to ten volunteers were instructed in their jobs, the children were filed into the room by their teachers. The classes came at staggered times so that a continuous line was maintained. Each child held his own registration-parental permission slip.

At the first station each child to be tested had his anterior forearm washed with distilled water and dried with gauze. The prepared area was covered with a $4 \times 4''$ square of parafilm, and a heated aluminum cylinder (temperature of 48° C.) was placed on top of the parafilm to stimulate sweating. As soon as this was accomplished, the time was recorded on the child's registration slip so that an exact stimulus period of five minutes could be determined. The registration slip was then returned to the child.

As soon as the child's five-minute period was up, the technician's assistant placed the child's arm convenient to the technician and equipment and removed the heat stimulus and parafilm. At the same instant the chloride ion electrode was placed on the sweat on the forearm, and the meter reading was obtained and recorded on the child's registration slip.

This coordinated procedure permitted about 200 children to be tested each hour. Preschoolers required additional time and attention.

Children with sweat chloride test values of less than 30 mEq/L were judged to be normal and were discharged from the detection clinic. Children with a sweat chloride test value of over 30 mEq/L were judged suspects and were retested. If one or more test results were greater than 40 mEq/L the child was selected for retesting with pilocarpine iontophoresis.

Results

Between February and May of 1966, the screening sweat test program for cystic fibrosis was conducted in 26 cities and towns in Minnesota. The communities participating and the number of children tested in each are listed in Table 1.

TABLE 1

DATES	CITY	# TESTED
2-8-66	Shakopee	1,159
2-15-66	St. Charles	411
2-16-66	Stewartville	602
2-21, 22-66	Moorhead	1,373
3-1, 3-66	Detroit Lakes	927
3-3, 9-66	Owatonna	1,156
3-17-66	Milaca	513
3-18-66	Mora	315
3-21, 22, 23-66	Willmar	2,220
3-24-66	Glenwood	579
3-29, 30-66	Fergus Falls	811
3-31, 1-66	Northfield	995
4-12-66	Madelia	509
4-13-66	Truman	247
4-19, 20-66	Fairmont	796
4-21-66	Jackson	533
4-22-66	Windom	586
4-27-66	Wheaton	465
4-28-66	Elbow Lake	418
5-2, 3, 4-66	South St. Paul	1,755
5-11-66	Park Rapids	469
5-12-66	Ely	496
5-17-66	Pipestone	596
5-18, 19-66	Hastings	1,174
5-24-66	Redwood Falls	452
5-25-66	Granite Falls	514
Totals	26 Communities	20,071 Children

List of cities in which C.F. Detection Clinics were held with dates of testing and number of children tested.

Participation varied from community to community. In one school system all the children in the selected grades received permission from their parents to have the sweat test. In another school only half the children received permission. Nevertheless, on the average almost 95 percent of the children in school received parental permission to be tested. Class attendance varied from grade to grade and school to school from 90 to 100 percent with an estimated 95 percent attendance. Therefore, between 90 and 95 percent of the children whom we planned to test were tested.

TABLE 2
Age Distribution of Children Tested

Age	% of all Children	# of Children with High Chloride Tests
0-1	2	0
1-2	3	2
2-3	5	3
3-4	5	2
4-5	5	3
5-6	12	4
6-7	21	19
7-8	23	14
8-9	16	10
9-10	5	1
10-11	5	0
11+	1	0

Age and Sex

Equal numbers of boys and girls were tested. The age distribution by sex was the same as that of the total group shown in Table 2.

On the initial sweat test nearly 1,500 children (seven percent of the total tested) had sweat chloride values greater than 30 mEq/L. On retesting in the clinic 57 (¼ of one percent) were found to have persistently high sweat chloride values. The age distribution of children with high sweat tests was comparable to that of the whole group but there were 2½ times as many boys as girls with high sweat chlorides. Thirty-six of the high sweat chloride values occurred in two cities. These children were retested later in the spring with the pilocarpine iontophoresis technique.[7] On this third testing only two were found to have high values. These children and their families were studied in detail.

Increased Sweat Chloride

All of the members of family H (Figure 1) are in good health. The increased sweat chloride in R.H. detected in the Cystic Fibrosis Detection Clinic was confirmed by pilocarpine iontophoresis technique.[7] However, when R.H. was encouraged to use less salt on his food his sweat test values dropped into the definitely normal range. Final diagnosis was excessive salt intake in a normal child.

All members of family J (Figure 2) are in good health. The increased concentration of salt in the sweat found by the Cystic Fibrosis Detection Clinic was confirmed by the pilocarpine technique. All the tests done on the three oldest children including the suspected one have been in the high five percent of sweat chloride values for our laboratory. One child had several tests intermediate between normal and cystic fibrosis, but the latest ones are in the

		Mr. W. H.			Mrs. B. H.
7-18-66		33,42,33,39			40,43,38,40
4-16-67		46,48,38,41			8,11,12,13
	R. H. (8 yrs.)	K. H. (7 yrs.)	T. H. (4 yrs.)	M. H. (4 yrs.)	S. H. (3 yrs.)
5-10-66	51,54	33,34	....	39,43	....
5-31-66	46,47,49,60	27,25,22,26	20,22,19,20	26,29,36,37	17,26,26,19
7-18-66	32,35,33,28	....	....	....	....
4-16-67	33,36,29,35	18,14,16,17	12,14,11,6	24,16,30,15	99,5,8,6

Fig. 1. Results of Sweat Chloride Study (Pilocarpine Iontophoresis) on Family H

		Mr. J. F. J.			Mrs. A. J. J.
10-19-67		55,63,63,65			7,5,4,8
	J. J. (7 yrs.)	A. J. (6 yrs.)	K. J. (5 yrs.)	M. J. (4 yrs.)	D. J. (2 mo.)
6-9-66	....	44,49,50	....	....	....
8-8-66	39,39,39,44	38,48,49,51	....	18,25,26,30	....
8-11-66	....	....	31,32,35,38	....	6,8,10,11
10-19-67	33,27,37,32	37,34,33,35	31,27,32,28	12,12,18,12	....

Fig. 2. Results of Sweat Chloride Study (Pilocarpine Iontophoresis) on Family J

high normal range. Our tentative diagnosis is normal child with excessive salt intake or familial tendency to salt loss in the sweat.

Fluctuation in Line Voltage

The three children living in these cities who were known to have cystic fibrosis were tested as positive controls. When one was missed by the testing team a review of the technique and an investigation of the equipment were made. Thus we discovered that under certain previously unknown circumstances, fluctuations of line voltage at the time of the sweat test could cause spuriously high values in some normal children or low values in some children with cystic fibrosis. As the unsuspected difficulty was not discovered and corrected until near the end of the testing program, the possible prior occurrence of temporary dysfunction of the meter due to line voltage changes and the coincident testing of a child with cystic fibrosis could not be known.

In an effort to discover this as a possibility we wrote to all the doctors whose patients participated in the testing program to ask: Have you discovered any new patients with cystic fibrosis in the year since the sweat test program in your city? If yes, did the patient have a sweat test in the school cystic fibrosis sweat test program? A letter was sent to 162 physicians, of whom 139 or 85.8 percent answered. Three new cases of cystic fibrosis were found during the year: one child was born several months after the testing program; the second was about five years old and thus in the group of untested children. This patient has been lost to follow-up by the reporting physician. The third was a five-year-old sibling of a child with cystic fibrosis, whose parents decided not to bring him to the school in which the detection clinic was held. None of the three had been tested in the program.

Altogether these 139 physicians reported caring for 109 patients with cystic fibrosis in prior years. Since about 106,000 infants in these 26 community areas were born during the past 20 years, we derive a crude incidence estimate of 109 cystic fibrosis children per 106,000 newborn infants or one child with cystic fibrosis in 970 newborn infants.

Analysis

Assuming an incidence of one case in 1000 newborn infants, 20 children were born into the group of children tested. Since the cumulative mortality from cystic fibrosis in patients not receiving pulmonary therapy is 70 percent by age seven we estimate that six should have been alive in these communities and detectable in the group. Three known patients resided in the towns listed and were in the grades tested. If these assumptions are correct and the test was effective, we should have found three others. But we found only two suspects, both of whom were found to be normal.

The difference between the finding of no new patients in the sample tested and the expected three could be the result of:

1) Chance
2) Failure to test all the children, the patient with cystic fibrosis being in the non-tested group
3) Error in estimate of mortality
4) Error in estimate of incidence
5) Failure of the test

Chance?

If the true prevalence of *undiagnosed* cystic fibrosis in a mixed group of children, average age seven (see Table 2), in Minnesota is three cases per 20,000 we would expect to find no cases once every five times we tested a sample of 20,000. Thus, our results are a probable and expected chance variation and the assumptions are not disproven.

Failure to Test All the Children?

Since about five percent of the children scheduled to be tested were absent on the day or days of the testing program and since about five percent of the parents refused to have their children tested, the tested cohort represents about 90+ percent of the actual cohort. Although this is a very large proportion, it may still be a biased sample.

Failure to have all the children present when the testing was done resulted in failure to detect two cases. To get cooperation from all the parents for this type of project is an almost insurmountable obstacle of potential significance to any large-scale testing program. That the small fraction missed in this study appears

to have affected the results tends to confirm this postulation.

Refusal of testing would have had no effect on the test if refusal were only a randomly-occurring bias against any testing program, but we do not know whether or not some parents refused to have a child tested because they suspected that the child might have the disease. That a group of absentees may include children with cystic fibrosis is to be expected, for children with cystic fibrosis who do not receive prophylactic pulmonary therapy are ill more frequently and miss more school than normal children. Any future population screening programs will have to include a technique for testing all children in the population, since even a random, unbiased sample of the healthy children would miss the child with cystic fibrosis who was sick on the day of testing.

Error in the Estimate of Mortality?

A life expectancy table for children with cystic fibrosis in Minnesota shows the expected mortality by age one year to be 36 percent, by seven years to be 70 percent.[2] A higher mortality rate is indeed possible; Dr. Norman's calculations suggest that the survival to age seven could be less than 20 percent[8]; but without more complete data a higher mortality cannot be proven. Yet the possibility emphasizes the need for perfection of a test for cystic fibrosis in the newborn period.[1]

Error in the Estimate of the Incidence?

Failure to find the expected number of cases of cystic fibrosis could be explained by too high an estimate of the number born. A corrected estimate based on the three known cases plus the two later discovered and our mortality estimate would be one in 1200 newborns. The corrected estimate is within the acceptable range of one in 1000 to one in 2000 newborn infants and not significantly different from our original assumption. Final certification or further correction of our estimate awaits the widespread utilization of the chloride ion electrode sweat test in the newborn nursery.[1,9]

Failure of the Test?

In over three years' use in our laboratories, the chloride ion electrode sweat test correctly identified every new case of cystic fibrosis and every normal child. Every chloride ion electrode test in the laboratory has been followed with the pilocarpine iontophoresis sweat test for confirmation. Since the testing conditions in mass testing situations were less well controlled than those in the laboratory, some decrease in accuracy was predicted. Most of the anticipated problems developed and were all solved during the months of testing. The malfunction of the meter caused by turning on fluorescent lights or by large fluctuations in line voltage was unexpected and was discovered only near the end of the testing program. All in all, it is impossible to disprove the possibility that such test failure occurred and led to failure to detect one or more children with cystic fibrosis. However, as great precautions were taken to have a "fail-safe" test and in view of the proven accuracy of the test in the laboratory this does not seem likely. Moreover, the failure to find even one case among the tested patients during the year after the program in which two nontested children were found to have cystic fibrosis provides strong, although negative, support for the reliability of the test.

Discussion

Although the ease, speed, and accuracy of this test indicates that it is the best available for population screening, the few children expected to be found alive and undiagnosed by school age and the rather large investment of time, effort, and money required suggest that routine screening of school-age children is not to be recommended. Nevertheless, the technique is applicable for large-scale screening programs designed to answer specific questions or as a preliminary survey prior to setting up routine nursery testing. The lessons learned and the improvement in equipment and technique which grew out of the survey establish this technique as the best available way to do accurate population surveys for cystic fibrosis. That no children with cystic fibrosis were found in the testing program and only three were found by physicians in these cities during the following year supports our predictions suggesting that the early mortality from cystic fibrosis is as high as—perhaps higher—than our estimates.

Conclusions

Two conclusions are apparent: First, the screening should best be done at an age when the greatest likelihood exists that the child born with cystic fibrosis is still alive; thus, newborn screening is most to be desired. After that in decreasing order would be older infants, pre-school, and grade-school children. Testing junior or high school students would appear to be of little value since most children with cystic fibrosis not receiving pulmonary therapy would be expected to be dead or diagnosed by age 10.

Second, that the costs of the present testing program are low enough to warrant recommendation for trials of newborn and infant screening to establish the validity of and techniques for newborn nursery screening on a routine basis. We believe that further large screening programs of pre-school and grade-school children may be of value in special circumstances but that it would be desirable to develop a less expensive technique for use in these older children.

When a newborn nursery sweat test for cystic fibrosis has proved to be practicable, we will be able to start our present treatment program at a time when great gains in survival are to be expected. Then we will do more research to simplify our treatment procedures so that they can be applied successfully by a large proportion of families and can be made more useful to other children with bronchitis, asthma, bronchiectasis, or pneumonia. Since it has been shown that most of the pulmonary treatments developed for children with cystic fibrosis are of great value in the treatment of the other lung disorders in childhood, the earlier diagnosis of cystic fibrosis combined with controlled study of treatments may be expected to improve the health and perhaps save the lives of children with other lung diseases.

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9. Warwick, W. J.: Early Diagnosis of Cystic Fibrosis. GP 35:157, 1966.

Taxation

The art of taxation consists in so plucking the goose as to get the most feathers with the least hissing.—Ascribed to Colbert

---

There is a demand for men today who can make wrong appear right.—Terence 185-159 B.C.

Democracy

Democracy substitutes election by the incompetent many for appointment by the corrupt few.—Shaw

---

It is useless to close the gates against ideas; they overleap them.—Metternich

---

Statesman

A disposition to preserve, and an ability to improve, taken together, would be my standard of a statesman.—T. Burke



Meetings and Announcements

New ideas can be good or bad, just the same as old ones.—Franklin D. Roosevelt

JANUARY

American Academy of Orthopaedic Surgeons, [E], Palmer House, Chicago, January 20-25. Exec. Sec.: John K. Hart, 29 E. Madison, Chicago 60602.

American Group Psychotherapy Association, [E] La Salle Hotel, Chicago, January 24-27. Adm.-Sec.: Mrs. Marilyn Schiff, 1790 Broadway, New York 10019.

American Rheumatism Association, (Interim Meeting) Baltimore, Md., January 17-18. Info.: Miss Margaret M. Walsh, 1212 Avenue of the Americas, New York 10036.

American Society for Surgery of the Hand, Palmer House, Chicago, January 19-20. Sec.-Treas.: Raymond M. Curtis, M.D., 2947 St. Paul St., Baltimore 21218.

Health Physics Society, Midyear Topical Symposium (Sponsored by the Savannah River Chapter) "Environmental Surveillance in the Vicinity of Nuclear Facilities," Augusta Town House, Augusta, Ga., January 24-25. Info: Arrangements, Chmn., J. H. Horton, Radiological and Environmental Sciences Div., Savannah River Lab., Aiken, S. C. 29801.

Los Angeles Radiological Society (20th Annual Midwinter Conference) International Hotel, Los Angeles, January 27-28. Info.: Duane I. Gillum, M.D., Good Samaritan Hospital, 1212 Shatto St., Los Angeles 90017.

Research Study Club of Los Angeles Annual Midwinter Convention, in Ophthalmology and Otolaryngology, Statler Hilton Hotel, Los Angeles, January 21-26. Sec.: Burns C. Steele, M.D., 1411 W. Olive Ave., Burbank, Calif. 91506.

Society of Thoracic Surgeons, [E], Roosevelt Hotel, New Orleans, January 29-31. Exec. Sec.: Frances X. Byron, M.D., City of Hope Medical Center, 1500 E. Duarte Rd., Duarte, Calif. 91010.

FEBRUARY

American Academy of Allergy, [E], Statler-Hilton, Boston, February 3-7, Exec.-Sec.: Mr. James O. Kelley, 756 N. Milwaukee St., Milwaukee 53202.

American Academy of Occupational Medicine, Marriott Twin Bridges Motel, Washington, D. C., February 7-9. Exec. Sec.: Bertram D. Dinman, M.D., Institute of Industrial Health, University of Michigan Medical Center, Ann Arbor, Mich. 48104.

American College of Physicians (Air Force Regional), San Antonio, Tex., February 15-17 Info.: Lt. Gen. Richard L. Bohannon, USAF, (MC), The Surgeon General, USAF, Pentagon Bldg., Washington, D. C. 20330.

American College of Physicians (Alabama Regional), Point Clear, Ala., February 23-24. Info.: Howard L. Holley, M.D., U. of Alabama Medical Center, 1919 7th Ave. S., Birmingham, Ala. 35233.

American College of Physicians (Northern California/Nevada Regional), Monterey, Calif., February 16-17. Info.: Roberto Escamilla, M.D., 897 Hyde St., San Francisco, Calif. 94109.

American College of Physicians (Southern California Regional), Palm Springs, Calif., February 23-25. Info.: W. Philip Corr, M.D., 3660 Arlington Ave., Riverside, Calif. 92506.

American College of Physicians (Hawaii Regional), Honolulu, February 21. Info.: Morton E. Berk, M.D., 1133 Punchbowl St., Honolulu 96813.

American College of Physicians (Kansas Regional), Topeka, Kan., February 23. Info.: Sloan J. Wilson, M.D., U. of Kansas Medical Center, Kansas City, Kan. 66103.

American College of Physicians (Nebraska Regional), Lincoln, Neb., February 3. Info.: Henry J. Lehnhoff, Jr., M.D., 720 Doctors' Bldg., Omaha, Neb. 68131.

American College of Psychiatrists, Fontainebleau Hotel, New Orleans, February 2-3. Sec.-Gen.: J. Martin Myers, M.D., 111 N. 49th St., Philadelphia, 19139.

American College of Radiology, [M], Drake, Chicago, February 6-10. Exec. Dir.: William C. Stronah, LL.B., 20 N. Wacker Dr., Chicago 60606.

American College of Cardiology, [E], San Francisco Hilton Hotel, San Francisco, February 28-March 3. Exec. Dir.: William D. Nelligan, 9650 Rockville Pike, Bethesda, Md. 20014.

The Nobel Conferences

Fourth annual Nobel Conference is to be held January 10-11, Gustavus Adolphus College in St. Peter. The 1968 theme is "The Uniqueness of Man."

Contact: James Wennblom at the College for information.

Continued from Page 150.

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Kevin Is a Hippie

(Continued from Page 61)

finds us and our loved ones well and happy, and the entire Hoppworth Family joins in expressing the most heartfelt wish that every good thing may be yours throughout the coming year."

A final embellishment that will go far towards the construction of a really first-rate Christmas Letter is the enclosed photograph. This may be a snapshot of a new yacht or western ranch, but nothing can compare in effectiveness to the family group photograph. The group must include all members and it is imperative that everyone be smiling. Remember that a heavy set of dental braces is an indication of family commitment to better living and will go a long way to presenting an image of a Family Who Cares. If at all possible the family pet or pets should be included. I usually borrow a neighbor's cat because I have noticed that poets and other intellectuals seem to show a preference for cats, but a dog or dogs will do as well; if a fine saddle horse can be seen grazing in the background, so much the better.

There you have the barest rudiments of a Christmas Letter. The choice of color of paper and ink I leave to you. It is my hope that this little essay may be valuable, even inspirational to Christmas Letter authors of all degree of proficiency. I foresee the day when the mailmen of America will bend low beneath a burden of truly beautiful Christmas Letters from almost every family in the nation.

E. A. Doherty, M.D., W.

Psychology has its Gresham's Law; its bad money drives out the good. Most people tend to perform the actions that require least effort, to think the thoughts that are easiest, to feel the emotions that are most vulgarly commonplace, to give the rein to desires that are most nearly animal.—Aldous Huxley

---

In eating, a third of the stomach should be filled with food, a third with drink, and the rest left empty.—Talmud



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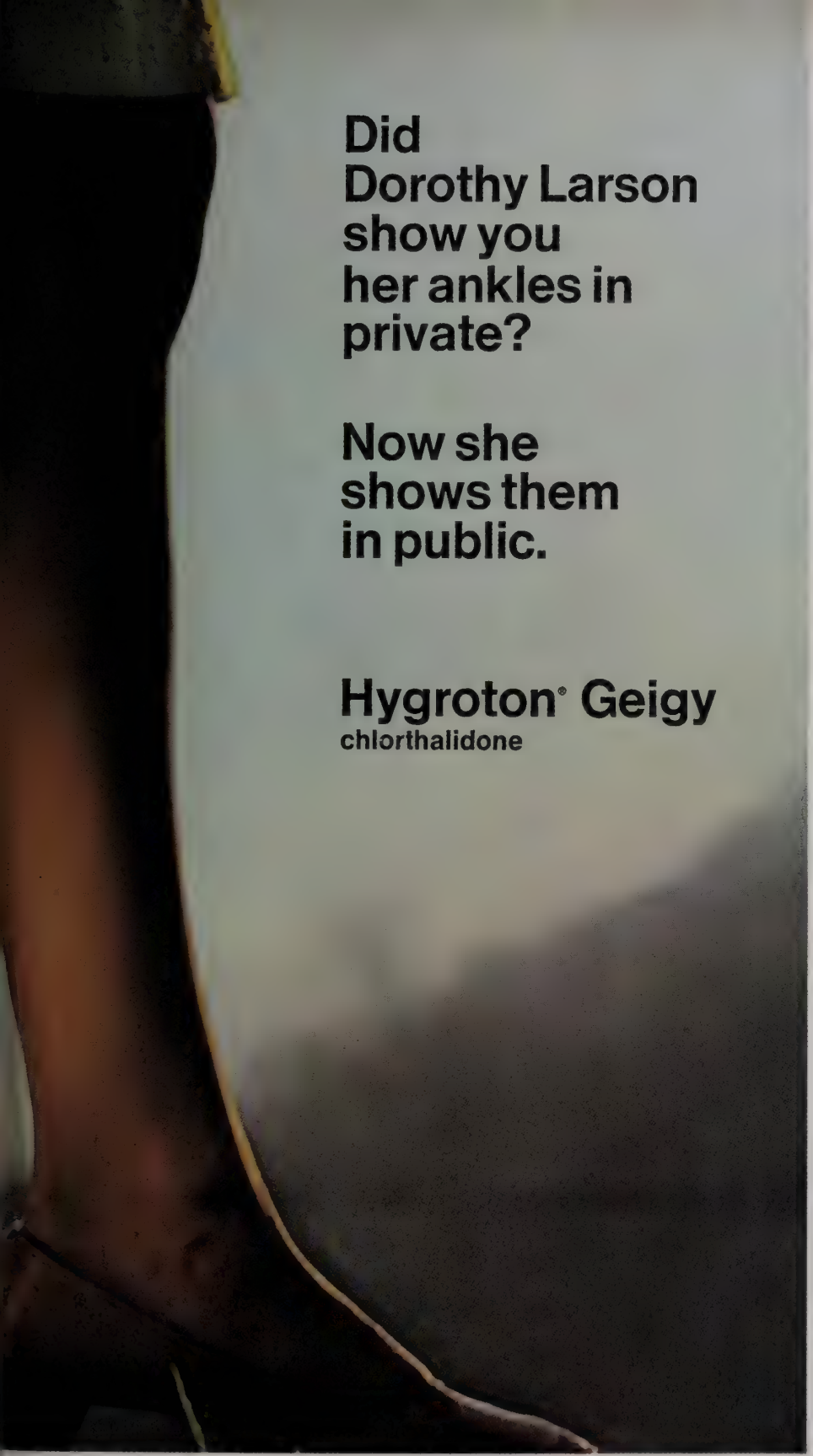
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or potassium depletion may oc
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Minnesota Medicine at a Glance

Prophylaxis in Oral Surgery—Waite, et al. Page 21

This article deals with the prophylactic administration of antibiotics in the course of oral surgery. The studies indicate that the use of an antibiotic does diminish the bacterial content of the blood which was observed after oral surgery.

Chronic Obstructive Airway Disease—Dines and Fowler Page 33

Two simple office or bedside procedures can effectively screen most ventilatory problems. Inability to blow out a paper match at 6 inches correlates well with a one-second vital capacity of 1500 ml. or less, and a maximum breathing capacity of 40 liters per minute. Also described is the bellows-timed vital capacity. Both tests are correlated with pulmonary function studies.

D. Pneumoniae—Shope and Quie Page 37

This article is about a pediatric patient with recurrent staphylococcal infections and with fatal pneumococcal pneumonia. The pneumococci isolated from the blood showed an increased resistance to oxacillin. The need for sensitivity studies is stressed.

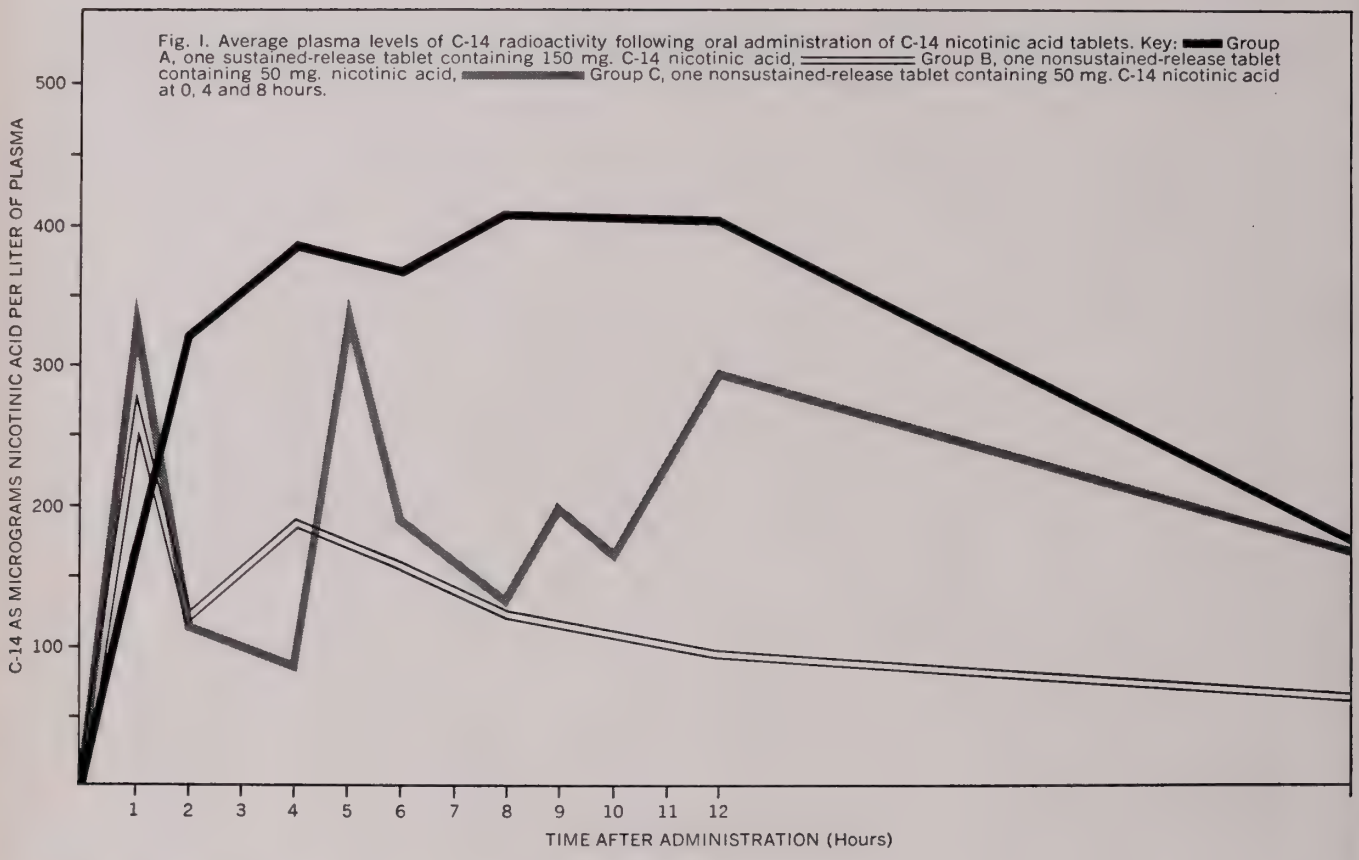
Traumatic Rupture of the Testicle—Wedge and Blackard Page 73

Traumatic rupture of the testicle should be suspected in every scrotal injury resulting in swelling and induration of the scrotal contents. Prompt surgical decompression of the hematoma and debridement of devitalized tissue will likely result in a greater salvage of functional testicular tissue.

Cystic Fibrosis—Warwick and Koroshec Page 153

Over 20,000 children were tested for cystic fibrosis in a school sweat test screening conducted in 1966. Although no new cases were discovered in the tested group, three new cases were discovered among non-tested children in the year after the Cystic Fibrosis Detection Clinics were held. These findings support the prior assumptions that one child is born with cystic fibrosis among each 1000 newborn infants and that over 70 percent of these children not receiving pulmonary therapy, die before age seven. These findings also suggest that now is the time to begin trials of newborn nursery screening for cystic fibrosis.

Sustained circulatory, respiratory and cerebral stimulation for the





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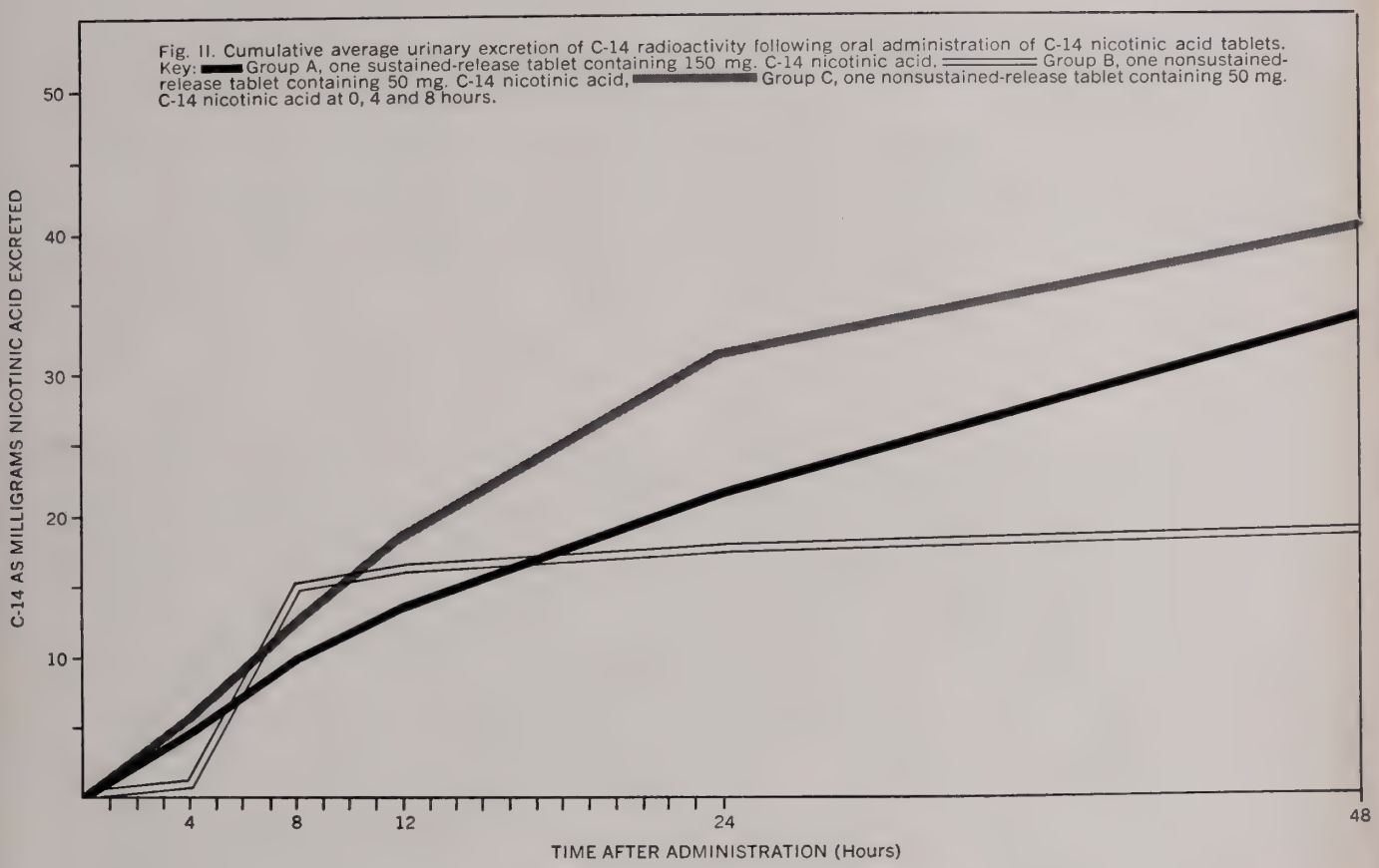
Human volunteer subjects were administered Geroniazol TT tablets with the nicotinic acid component made radioactive with C-14. Plasma and urine samples were analyzed. (See Figures I and II) The radioactive tracer study substantiated the previous clinical evidence that the release of nicotinic acid from the Geroniazol TT tablet produced a gradual rise in plasma levels to a plateau for a total of 12 hours and more.

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References: 1. Report by Nuclear Science & Engineering Corp., Pittsburgh, Pa., in files of Philips Roxane Laboratories. 2. Connolly, R.: W. Virginia Med. J. *56*:263 (Aug.) 1960. 3. Curran, T. R., and Phelps, D. K.: Am. Pract. & Digest Treat. *11*:617 (July) 1960.

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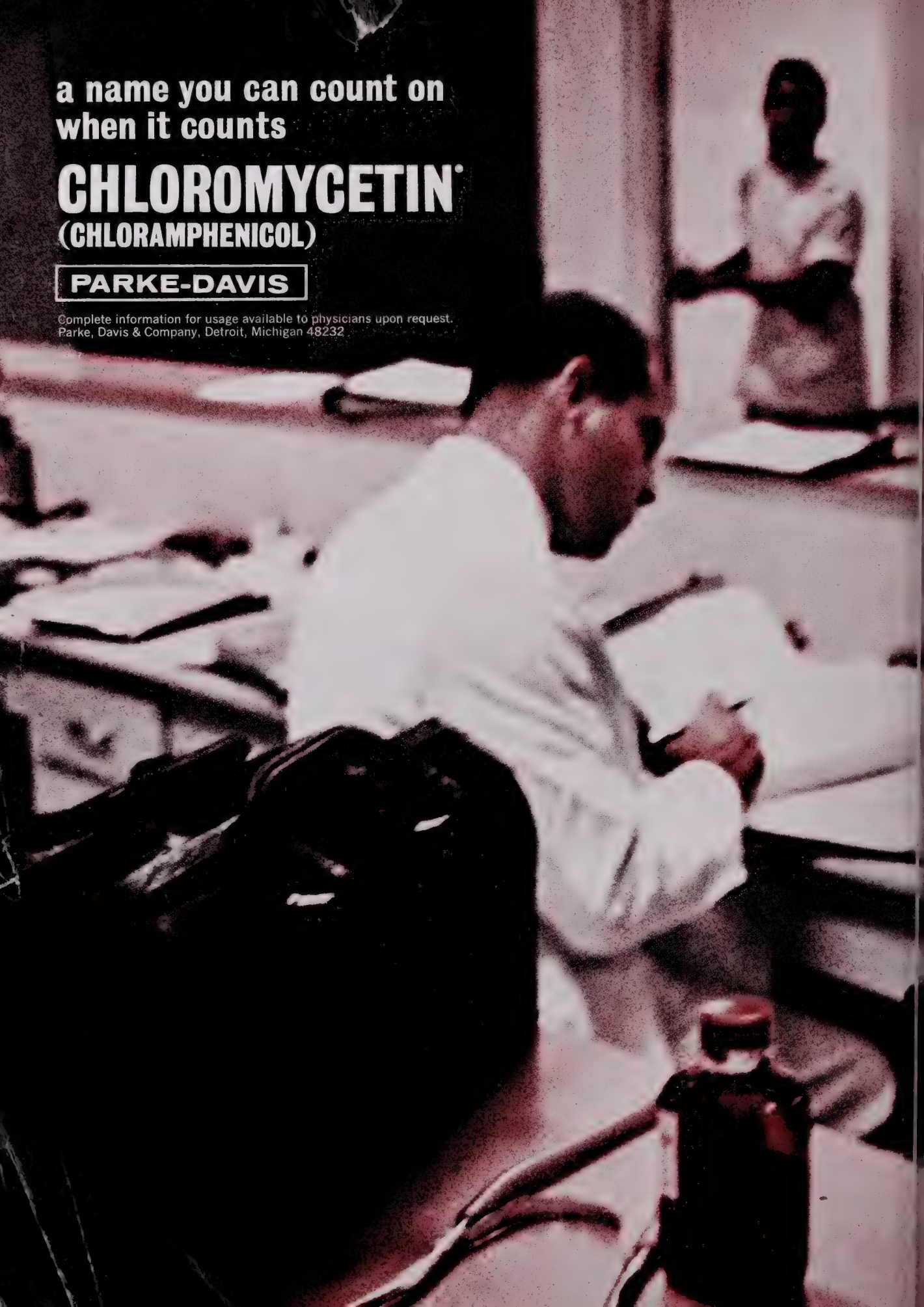
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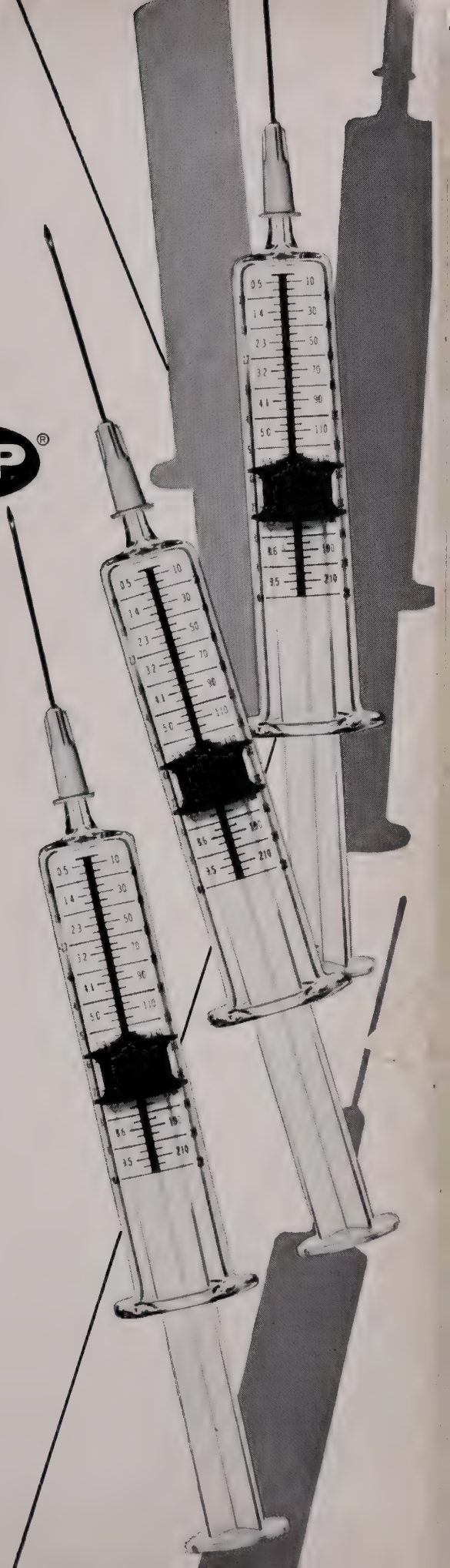

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President's Letter

PERHAPS AT NO other time in the history of medicine have we been faced with so many profound changes within the Profession. These changes have involved medical education, patterns of practice, payment for medical care, and the delivery of medical services.

We have seen, in the last quarter of a century, the dwindling number of solo practitioners and the extensive development of group practices. We have become aware of the decreasing number of small-town physicians and the tendency of physicians to congregate in the larger communities. We have seen the decreasing number of privately endowed hospitals and the development of the hospital financial structure based on sound business principles. We have seen the emergence of prepayment medical care plans and more recently have witnessed the entrance of Federal Government into the field of medical care.

The information explosion which has deluged us with knowledge has merely whetted our thirst for more. It introduced us to specialization as a means of better cataloging this knowledge and as a useful tool for further research. The use of the same fragmentary approach to the delivery of medical care has met with recent public and professional rebuff as documented by the Millis and Willard reports.

We, in medicine, must learn to be responsive to the public demands. The public, our patients, are rapidly becoming much better medically educated and much more sophisticated in their attitudes toward medical care and these demands. In many cases it will be difficult to resolve conflicts between demands, needs, and feasibility.

To do this effectively and still maintain physician control of the Medical Profession will require that the quality of medical care available be of the highest caliber. To do this we will need a vast expansion in our Postgraduate Education Programs. The possibility of recertification examinations, such as the American Academy of General Practice is planning to initiate, with the proposed American Board of Family Practice, will undoubtedly be one means which may have to be applied to other segments of the Medical Profession.

More attention must be paid to the delivery of medical care. Included in these studies would be not only the development of more efficient ways to adequately take care of more patients per physician, but also the methods by which physician's services could be made available to certain areas which consistently have inadequate physician coverage.

We can no longer sit back and complacently contemplate the fine record of American Medicine. We must anticipate the public needs and learn to respond to public demands in a manner calculated to fulfill public requirements and improve overall medical care. This of course also implies that we physicians must organize ourselves well enough to more effectively cope with third-party intervention into medical care: not from a defensive stance, but with an aggressive forward-looking program which will leave no vacuums to be filled by socialistic Government Programs.

Edward W. Ciriacy, M.D., President
Minnesota Academy of General Practice

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Lower Limb Amputations in Peripheral Vascular Disease*

Factors Influencing the Level

WILLIAM J. KANE, M.D., Ph.D.**
Minneapolis, Minnesota

THE PROBLEM of peripheral vascular disease necessitating amputation is a major health problem and is increasing. Sidney Fishman of N.Y.U. estimates that there are 400,000 amputees in the United States, and because of prolonged life spans there is an increasing incidence of amputations due to peripheral vascular disease.[1] In a recent survey by Glattly, 55 per cent of the persons presenting themselves for prosthesis† fitting were victims of disease, and it has been shown that only about half of the geriatric patients who have had major amputations present themselves for prostheses.[2,3] Accordingly, it can be safely maintained that over two thirds of the amputations performed in this country are due to peripheral vascular disease, considering that Glattly's classification included infection in his "disease" category and recognizing that amputations about the foot and toes do not usually require prostheses.*

The purpose of this paper is to discuss some of the factors which influence the level of amputation in patients with peripheral vascular disease.

Amputations in peripheral vascular disease are performed to remove infection, gangrene, and pain, and consequently to preserve health and life and to improve function. Function following an amputation is largely dependent upon the level of amputation and whether a prosthesis is used. The general principle of amputation surgery is to save as much limb as possible consistent with the control of the disease process; practical experience is required to apply this principle in specific situations. It is also necessary to consider briefly prosthetic-fitting criteria, for this problem is intimately connected with the level of amputation.

Contraindications to Prostheses

It is generally felt that certain factors represent absolute contraindications to limb-fit-

*See editorial page 209.

**Assistant Professor, University of Minnesota Medical School, Department of Surgery, Division of Orthopedic Surgery, Minneapolis, Minnesota.

†See Test Your Word Score Page 217.

ting and that, therefore, the usual necessity to preserve limb length is removed. These factors include:

1. Lack of motivation
2. Impending gangrene of the other leg
3. Serious cardiac condition—Class IV
4. Severe neurological disorders
5. Multiple major physical disabilities
6. Known inadequate life expectancy.

Relative contraindications include:

1. Senility
2. Inability to use upper extremities
3. Extreme obesity
4. Severe flexion deformities
5. Intercurrent disease[4,5]

A word of caution about these contraindications. It may be quite difficult to establish that a patient is truly lacking in motivation; the patient's dejection at the impending amputation may obscure his genuine desire to wear a prosthesis. In most instances, the geriatric patient should be approached in a positive manner regarding his potential for using an artificial limb. It must be recognized that many such patients will not function at a level considered adequate when compared to preamputation levels; nor should we anticipate that they will function at a level which is established for younger patients. Such levels of achievement are not required for successful rehabilitation of the geriatric patient.

The use of an artificial limb is an additional tax on the cardiac reserve and the peripheral vasculature. It requires at least 20 to 25 per cent more energy for a unilateral above-the-knee amputation to cover a given distance than it does to walk on two normal legs.[6] Therefore, one has to evaluate the cardiovascular system carefully to prevent this additional expenditure from bankrupting the geriatric physiology.

The goals of amputation surgery are to preserve life and maintain health by eliminating infection and necrosis, to improve function and eliminate pain, to obviate the need for further amputations and possibly to allow the use of prostheses. In serving these aims the surgeon faces the dilemma of deciding which is the optimal site for amputation. The hope of saving as much tissue as possible is tempered by the realization that the more proximal the amputation, the quicker the healing; and until recently it was fairly obvious that surgeons were more frequently solving the question by going to the higher amputation sites. Glattly, in his review of the amputee census, discusses a group of 4500 above-knee and below-knee amputations for disease. He states: "It may be that too many surgeons are overly concerned with the possibility that amputations at the below-knee level will later require re-amputation above the knee. This possibility is suggested by the fact that in this series there were only 12 instances in which below-knee amputations due to disease were re-amputated at a later date. This is an extremely low incidence, considering the number of below-knee amputations that are performed for vascular conditions. A clinical study may be needed that is designed to define better the criteria that bear upon the decision as to the level of amputation in cases of lower extremity vascular disease. The advantages of preserving the knee joint are obvious, especially in the older age group."[2]

Levels of Amputation

The selection of the appropriate level of amputation in the geriatric patient with vascular disease should be based entirely on the level of vascular sufficiency in the extremity. By vascular sufficiency is meant that healing of the tissues will follow surgery, and the only reliable guide to this is free bleeding at the time of the amputation. There are, of course, other indicators which are helpful, but they are only relative. These signs are skin temperature and color, absence of trophic changes, palpable pulses, rapid venous filling time and reactive hyperemia. Regression of local infection, a sharp line of demarcation, and the absence of rubor on dependency at the amputation site also portend a successful amputation.[5] Of the various mechanized tests available, probably oscillometry is the most easily used clinically.[7] X-rays of the pelvis and upper portion of the thigh also give information regarding the state of calcification in the arterial tree, and angiograms may indicate the feasibility of peripheral by-pass grafting with venous grafts.

Attention will first be directed to the prevention of amputations. Impending gangrene

may be substantially improved by venous grafts where there is a popliteal run-off. While this is a possibility in arteriosclerotic disease, it is usually unsuccessful in peripheral vascular disease complicated by diabetes, for in diabetes not only does the arteriosclerotic process occur, but there is the concomitant endothelial swelling and occlusion which prevents collateral circulation from developing. For the same reason, sympathectomy is believed to offer little to the diabetic.[8] Endarterectomy in the more proximal vessels also benefits some of the arteriosclerotics uncomplicated by diabetes. In a like manner, meticulous wound care with frequent baths in detergent followed by gentle drying, the avoidance of trauma, rest, treatment of the cardiovascular disease and cessation of smoking may avoid an amputation.

Local Toe Level

If local toe infections do not respond to conservative management, amputation of the toes should be considered under the following conditions:

1. Only one toe involved with a terminal ulcerative or gangrenous lesion that is well demarcated and stabilized after several weeks of rest.

2. Lesions at the level of the middle phalanges of the second, third, and fourth toes will not respond to toe amputation, since these toes should be amputated through the proximal phalanx.

3. Willingness on the part of the patient and surgeon to invest three to 10 weeks in preoperative preparation in the face of a 45-per cent failure rate.

Toe amputations are contraindicated if pulses distal to the femoral vessel are absent, and if uncontrollable rest pain and dependent rubor are present.[5,9,10]

It is wise to avoid a prolonged hospital stay in such situations, because most of these patients with diabetes will develop gangrene in the opposite limb or succumb to their cardiovascular disease, and morale can deteriorate rapidly in prolonged confinement.

Transmetatarsal Level

If the conditions for a solitary toe amputation are not met, the next level is the transmetatarsal, which offers many advantages over a below-knee amputation. It is a minimum handicap, requiring no prosthesis and causing little additional contralateral limb strain. Transmetatarsal amputations should be considered when:

1. Stabilized distal gangrene not involving the dorsal or plantar surfaces of the forefoot is present in a healable foot, with circulation sufficient to control gangrene with bed rest, antibiotics, and diabetic control.

2. There is no ischemic foot pain on rest, no dependent rubor, and a venous filling time of less than 25 seconds.

3. The entire lesion can be excised and primary suture obtained. A transmetatarsal amputation is not an alternative after failure of a toe amputation.[5,11,12]

Recent evidence offers much hope that transmetatarsals give very acceptable results. Usually, 10 per cent are early, complete failures, but this is a reasonably low figure and the amputation may persist as long as two years. In one series of diabetics, 46 per cent of the living patients had intact incisions at five years; it must be noted, however, that only 23 per cent of the patients were alive at that time.[5,12]

Peripheral vascular disease does not lend itself to Syme's or hindfoot amputation; hence they will not be discussed.[5]

Below-Knee Level

The next level is the below-knee amputation which apparently is worthy of more consideration than it has received in the past in the treatment of peripheral vascular disease. It is not without some justification that surgeons elect the higher level. In one series of 83 above-the-knee amputations, 75 were satisfactory while only 27 out of 81 below-the-knee amputations were satisfactory[13] Given proper guidelines, though, the knee joint can be saved. Record, Smith, Kelly and Janes have enumerated some of these guidelines.[5,13,14] The advantages of a below-the-knee amputation include an apparent lesser mortality; but this may be the result of a biased selection in which the more severe problems are subjected to above-the-knee amputation. Below-the-knee amputations have better function with less contralateral stress than above-the-knee amputations, and their prosthesis if useable is

lighter. Balance is easier, as is turning in bed with a below-the-knee amputation.

General agreement can be reached by saying that a patient may be offered a below-the-knee amputation if the following criteria are met:

1. There is some hope of rehabilitation.
2. There is good bleeding at the amputation site with contractile muscle at that level and good warm skin to the middle of the leg and, if possible, to below the lower third.
3. A femoral pulse is palpable.

A palpable popliteal pulse is desirable, but if it is not palpable there should be oscillometric excursions in the calf. Kelly and Janes state that an absent femoral pulse and a history of sudden arterial occlusion absolutely contraindicate a below-the-knee amputation.[14] A slow onset of the disease rather than a sudden occlusion allows for satisfactory below-the-knee amputations. Obviously, a functioning knee joint is necessary.

It appears that age also has an influence on the results of surgery. In Smith's series, all patients under 52 years of age had good below-the-knee stumps; he also states that a palpable popliteal pulse usually promises a satisfactory below-the-knee amputation; but even in the absence of a popliteal pulse, 20 per cent will have worthwhile below-the-knee amputations if there are oscillometric excursions in the calf.[13]

In Kelly and Janes' review of 131 below-the-knee amputations, there were 31 severe wound complications, half of which were in patients with sudden arterial occlusion. The mortality rate for below-the-knee amputations was 3 per cent.[14] Most authors agree that stumps may be shorter in peripheral vascular disease and advise stumps of around four inches.[13] Smith points out that if a below-the-knee stump is going to give trouble it usually will do so in less than a year. If it does, do not revise the below-the-knee, for Smith found 100 per cent failure in 17 below-the-knee revisions of earlier below-the-knee amputations. For similar reasons, do not leave a long below-the-knee stump, planning on a shortened revision later. Do the below-the-knee amputation at the four-to-five inch level as the first procedure.[13,14]

Above-Knee Level

The indications for above-the-knee amputation obviously include the inability to meet the criteria necessary for amputation at the lower level and some absolute indications requiring an above-the-knee amputation:

1. Patients who can tolerate only one procedure or who have a diseased knee joint should receive the above-the-knee amputation as well as patients with unsuccessful below-the-knee amputations.
2. Patients with gangrene of the middle third of the calf or with extensive gangrene of the distal third of the calf.
3. Sudden arterial occlusions with weak or absent femoral pulses should indicate an above-the-knee amputation, as do sudden arterial occlusions with coolness of skin above the middle of the leg, high venous filling times, severe ischemia detected by elevation-dependency tests, and only fair bleeding at the below-the-knee site. The mortality for above-the-knee amputation is approximately 10%.[14]

Discussion

As the geriatric population increases and longer life-spans are achieved, an increased incidence of amputation due to arteriosclerotic conditions is anticipated. Many surgeons adopt an overly conservative approach to amputations about the toes and foot; but in amputations about the knee are perhaps overly aggressive, amputating above the knee in certain instances where below-the-knee amputations would have an excellent chance for success. Points that deserve emphasis are that sudden femoral arterial occlusions, with the corresponding lack of an opportunity to prepare collateral circulation, are indications for above-the-knee amputations, and that failures of below-the-knee amputations cannot be salvaged except by above-the-knee amputations.

Summary

Amputations for peripheral vascular disease are increasing. The indications for, and advantages of, each of the four chief levels of amputation are presented and should offer the surgeon planning an amputation a guideline to the level to be selected.

References may be secured from the author or the reprints.

A book is a mirror: if an ass peers into it, you can't expect an apostle to look out.—Lichtenberg

Acute and Subacute Fibrinopenic Syndromes

A Synthesis of Current Concepts

ROBERT B. BREITENBUCHER, M.D.*
Minneapolis, Minnesota

ACUTE DEFIBRINATION always represents a serious diagnostic and therapeutic challenge to the physician and a serious threat to the patient's life. Its manifestations are not usually heralded by any warning signals, nor is there any history of previous hemostatic dysfunction in the afflicted patients. Fortunately, the clinically manifest form of the syndrome is rare, although apparently a subclinical form may be found more frequently if carefully looked for.[1] The syndrome usually occurs as an obstetrical complication, although it may also be seen as a surgical complication, particularly in pulmonary surgery. Nothing creates more alarm than bleeding which cannot be stopped. By the same token, confusion ensues unless well planned diagnostic and therapeutic procedures are immediately available and put to use.

Review of Hemostatic Mechanism

The Vascular Wall

The first line of defense in hemostasis involves the integrity of the vascular wall. If a vessel is injured, the flow of blood to the vessel is reduced by constriction of afferent vessels. Contraction of the surrounding extravascular tissue produces some degree of compression which is helpful in stemming the flow of blood from the injured vessel.

Platelets pile up at the site and, if the injury is small enough, may patch the rent. Blood escaping through the rent forms a gelatinous coagulum which plugs the defect. Malfunction in any one will result in defective hemostasis.

The process of formation of the coagulum is a complicated and confusing one. In recent years this confusion has been largely cleared by an International Committee on Blood Clotting Factors. Figure 1 is a simplified schematic representation of the various factors listed in the probable order of action which eventually leads to the formation of insoluble fibrin, the structural matrix of the coagulum.

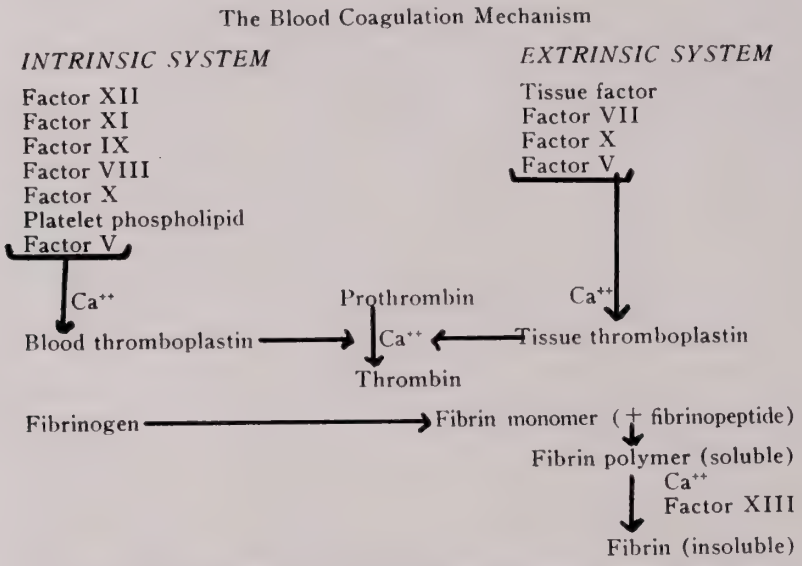
Body functions are often subject to check

*Chief of Medical Service, St. Mary's Hospital.

and balance systems; coagulation is an excellent example. Opposing coagulation is the fibrinolytic system activated partly by coagulation itself.

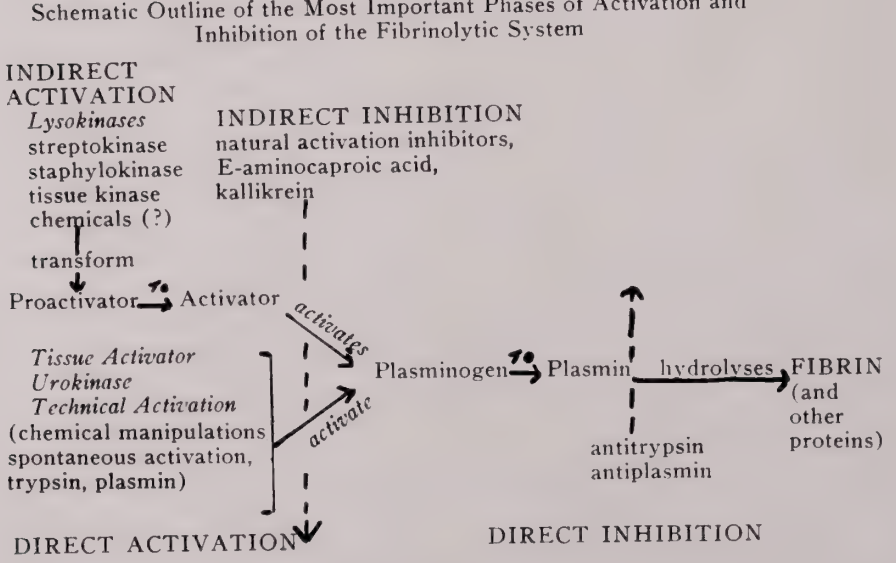
Fibrinolysis

The teleological explanation of fibrinolysis is that it serves to prevent too extensive coagulation and to reopen coagulated channels which have been closed in response to the emergency induced by blood loss. Many other conditions may also activate the system.[2] Figure 2 shows a schematic representation of the essential mechanics of the fibrinolytic system



From R. M. Hardisty & G.I.C. Ingram: Bleeding Disorders, Blackwell Scientific Publications, Oxford, 1965

Figure 1



From Kurt N. von Kaulla, M.D.: Chemistry of Thrombolysis: Human Fibrinolytic Enzymes, Charles C. Thomas Publisher, 1963

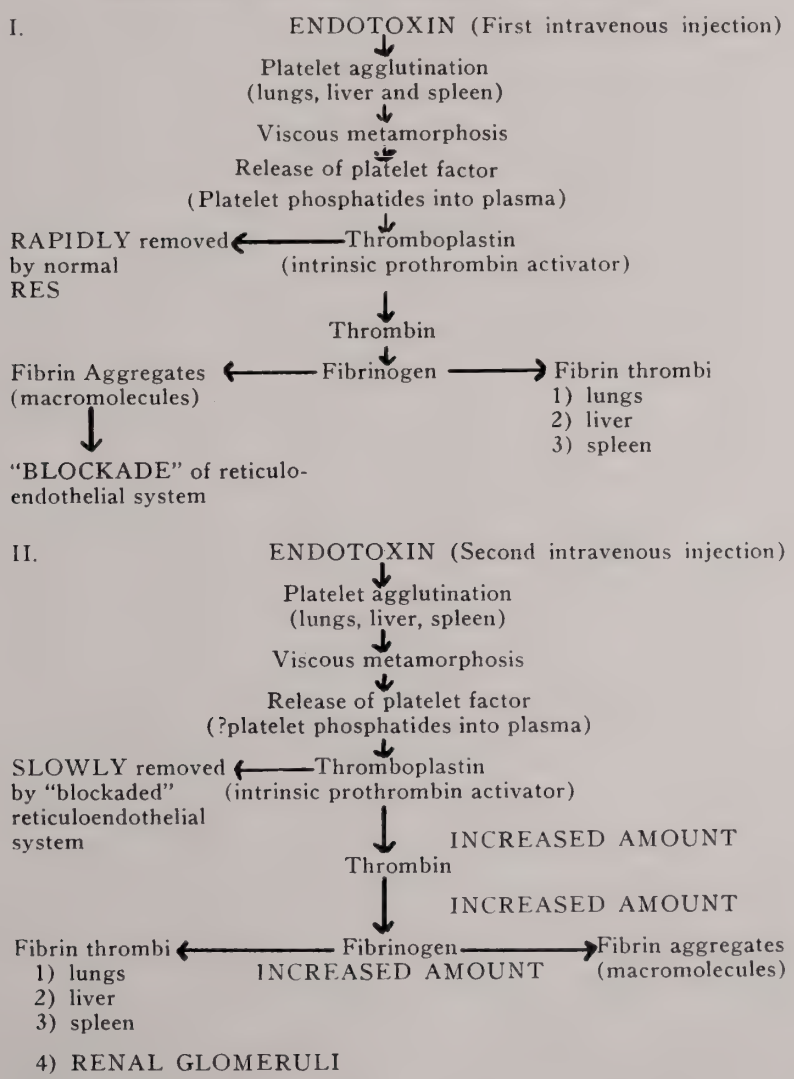
Figure 2

as it is recognized today.

Disseminated intravascular coagulation may result from activity of a variety of primary etiological factors, including hemolysis, tissue extracts, bacterial endotoxins, antigen-antibody complexes, proteolytic enzymes, particulate matter, anoxia, endothelial damage, fibrinolysin inhibitors, etc.[3]

Though the initiatory factors are diverse, the functional and pathological changes which follow are similar. Hypotension due to obstruction of blood flow through hepatic and pulmonary circulation by thrombi is almost always present. Changes in concentration of blood coagulation components used in the clotting process give results ranging from only transient platelet agglutination and thrombocytopenia in minor cases to severe depletion of fibrinogen, leukocytes, platelets, prothrombin, and factors VIII and IX. In the most severe cases a marked fibrinolytic activity appears which increases the depletion of factors I, II, V, VIII, IX. Depending upon the severity of derangement, hemorrhagic tendencies of varying degrees appear. When the clotting process is mild, platelet emboli may obstruct arterioles and capillaries only temporarily with no perma-

Mechanisms of the Classic Generalized Shwartzman Reaction



From Donald C. McKay: Disseminated Intravascular Coagulation, Hoeber Medical Division, Harper & Row Publishers, 1965

Figure 3

nent tissue damage. When the clotting process is severe, thrombotic obstruction of vessels leads to tissue necrosis of variable degree depending upon the extent of capil'ary clotting and whether or not large venous vessels become secondarily thrombosed. Lungs, brain, kidneys, adrenals, pancreas, gastrointestinal tract, and liver may be involved. The effects of disseminated intravascular coagulation which can be induced experimentally show a striking resemblance to those seen in various defibrination syndromes in human beings. But most of these effects can be either favorably modified or abolished experimentally by the administration of heparin.

The Shwartzman Phenomenon

Shwartzman found that if he prepared an animal by intravenous injection of a bacterial endotoxin and then re-injected the animal with the endotoxin in six to 24 hours, a sequence of events followed which in essence amounted to disseminated intravascular coagulation with the animal dying of characteristic renal cortical necrosis.[4] He also found that pregnant animals did not need a preparatory injection but would develop the syndrome after the first injection. It is postulated that preparatory blockade of the reticulo-endothelial system is obviated in pregnancy by the presence of increased amounts of factors I, II, V, VII, X, etc. The generalized Shwartzman phenomenon may also be produced experimentally in pregnant rats by feeding them an oxidized lipid diet.[5] Here there is a pathological development of degenerative areas in the placenta and of toxemia. The clot promotion is evidently initiated by placental clot-promoting agents in the degenerated areas of the placenta.

Particulate matter is also a factor in producing the generalized Shwartzman picture. Experimentally this condition can be produced by injecting amniotic fluid intravenously, but not by filtered amniotic fluid.[6] Other experiments done with colloidal suspension of materials such as kaolin and dextran have been used.[3,7] The colloidal material produces massive platelet agglutination, and the thrombotic sequence proceeds in the same manner as for bacterial endotoxin.

Clinical Problems

The clinical conditions where defibrination occurs are seen most frequently by the obstetrician. Premature separation of the placenta, retained dead fetus, amniotic fluid embolism, septic abortion, and hydatiform mole are conditions which the defibrination syndrome may complicate. It has been suggested that the syndrome may develop more commonly where there is some degree of toxemia of pregnancy.[8]

Premature Separation of Placenta

In premature separation of the placenta the mechanism is probably related to the fact that the placenta and decidua are rich in clot-promoting substance. Some of the cases of fibrinogenopenia appear to be due to generalized intravascular coagulation with defibrination. Perhaps others are due to deposition of large quantities of fibrin in the retroplacental clot.[9,10] Measurements of fibrin from these clots have been made with the quantity found adequate to explain the fibrinogenopenia. The presence of large amounts of the factors necessary in clot production is felt to lead to massive coagulation once the clotting cascade is started, which *per se* would overwhelm the reticulo-endothelial system.

Dead Fetus Syndrome

In females who harbor a dead fetus for longer than two weeks a gradual drop in fibrinogen frequently occurs. Actually a slight fibrinogen depression is usually seen in the days immediately following fetal death.[11] This is probably due to active retroplacental circulation absorbing clot-promoting products from the devitalized placenta. This phase does not produce serious fibrinogen depressions; in fact the fibrinogen level begins to rise again, probably because of a layer of fibrin being laid down between the devitalized placenta and maternal circulation. If the fetus remains undelivered, a second period of fibrinogen depression takes place. This is probably caused by degeneration of the ovular membranes which are no longer able to filter, but allow amniotic fluid particulate matter to enter the maternal circulation, with resultant clot promotion as mentioned in amniotic fluid experi-

ments in animals. Serious bleeding occurs in 1 to 2% of these cases. In the case of the dead fetus, the obstetrician may be forewarned of impending trouble by obtaining fibrinogen levels at weekly intervals as soon as a retained dead fetus is diagnosed.

Amniotic Fluid Embolism

Amniotic fluid embolism is a serious problem characterized clinically by the sudden onset of shock during labor or the first few hours after delivery. There may be a short prodrome of anxiety, restlessness, and vomiting. The patient becomes dyspneic and cyanotic, with signs of pulmonary edema. In patients who survive the initial period, a severe hemorrhagic diathesis develops. The initial phase is probably caused by marked platelet agglutination and platelet thrombi which block the pulmonary circulation. Serotonin liberated from the platelets could cause severe pulmonary vascular spasm as well. Knowing the clot-promoting ability of amniotic fluid, it is not hard to understand that there will be a decrease in factors I, II, V, VII, VIII, and in platelets, all concerned in the clotting process and leading to severe hemorrhage.

Septic Abortion

Septic abortion may be attended by fibrinogenopenia, hemorrhage, and other findings which parallel the Shwartzman phenomenon by endotoxin in the pregnant experimental animal.

Defibrination may occur temporarily in almost any surgical operation but is usually not of serious consequence. At times more serious defibrination may occur in operations on the lungs, which are rather abundant in coagulant material.

Metastatic Carcinoma

Metastatic carcinoma is sometimes responsible for activation of intravascular clotting or fibrinolysis. Hemangiomas may be associated with intravascular clotting and fibrin deposition within the tumor and activation of the fibrinolytic system. Intravascular hemolysis from mismatched blood, thrombotic thrombocytopenia, leukemia, snake bite, and drugs such as ristocetin* and dextran may all be associated with defibrination.[12]

*See Test Your Word Score Page 217.

Comments

It seems apparent in the majority of the instances of defibrination cited, the initial and most prominent factor seems to be coagulation with formation of fibrin. Other blood factors become depleted as they are consumed in the clotting process, so that the end result may be depletion of factors I, II, V, VIII, IX,

TABLE 1

International Nomenclature of Clotting Factors

I	Fibrinogen
II	Prothrombin
III	Thromboplastin (tissue extract)
IV	Calcium
V	Proaccelerin, labile factor, plasma ac-globulin
VI	Accelerin (a hypothetical intermediate product of the coagulation process; not now used)
VII	Proconvertin, stable factor, serum prothrombin conversion accelerator (SPCA), co-thromboplastin, auto-prothrombin I
VIII	Antihaemophilic factor (AHF), antihaemophilic globulin (AHG), antihaemophilic factor A, plasma thromboplastic factor A, alpha-prothromboplastin, thromboplastinogen, platelet co-factor I
IX	Christmas factor, plasma thromboplastin component (PTC), antihaemophilic factor B, plasma thromboplastic factor B, beta-pro-thromboplastin, platelet co-factor II, auto-prothrombin II
X	Stuart-Prower factor
XI	Plasma thromboplastin antecedent (PTA), antihaemophilic factor C, plasma thromboplastic factor C
XII	Hageman factor
XIII	Fibrin stabilizing factor (FSF), fibrinase

TABLE 2

Laboratory Investigation of the Defibrination Syndrome

Stage 1		Thrombin time Fibrinogen titre Platelet count	
	either Stage 1 tests normal but patient bleeding abnormally	or Stage 1 tests abnormal	
		Suggesting heparin	Suggesting defibrination
Stage 2	Prothrombin time	Protamine titration	Fibrinogen determination
	Partial thromboplastin time		Thromboplastin screening test
			Tests for fibrinolysis if indicated by fibrinogen titre, or otherwise thought appropriate
Stage 3	Assess effectiveness of treatment, and control subsequent course, by repeating those tests previously most abnormal or those relevant to treatment given.		

and of platelets in the circulating blood. When fibrin is formed, the fibrinolytic system will be activated. At times fibrinolysis seems to become an overwhelming factor and complicates the problem even further by lysis of other blood factors. Some of the products of proteolysis* are antithrombic, and heparin or heparin-like activity may be observed.

Appropriate laboratory studies are imperative but need not be complicated.

Diagnosis

A plan for study of patients suspected of having defibrination syndrome is presented in Table 2.

Stage 1 tests seek to establish four things: (1) the estimation of fibrinogen level, (2) the presence or absence of fibrinolytic activity, (3) the presence or absence of heparin-like activity, and (4) the platelet count. The status of fibrinogen, fibrinolysin, and heparin-like activity may be found by performing the thrombin time and fibrinogen titre with extended observations and modifications of these tests such as have been described by Hardisty and Ingram.[12]

After Stage 1 tests have been completed, further studies may then be helpful. The results of Stage 1 tests will determine the choice of these studies. If Stage 1 tests are normal, the problem most likely is related to a deficiency in the intrinsic or extrinsic system (Figure 1) other than fibrinogen or platelets. The prothrombin time and partial thromboplastin will be helpful here, and deductions may be made from the results of these tests (Table 2). If Stage 1 tests suggest heparin activity, a protamine titration will be helpful. If Stage 1 tests suggest the presence of defibrination, actual quantitation of fibrinogen will be helpful by gravimetric determination. The possibility of deficiency in other clotting factors may be estimated by performance of the thromboplastin screening test (Hicks-Pitney). Abnormalities of Stage 2 tests *per se* will not define the exact deficient factor(s). Hematologic consultation is probably indicated. For practical purposes of therapy, any factors which may be deficient as denoted by an abnormality in Stage 2 testing will be corrected by fresh plasma. As indicated in Table 2, Stage 3 results of therapy should be monitored by indicated studies.

*See Test Your Word Score Page 217.

Treatment

Therapy in the defibrination syndrome depends on the primary pathology and the type of hemostatic failure.

Removal of Causative Factors

Delivery by the natural route places considerably less demand on the hemostatic mechanism than caesarian section. It would seem desirable to allow natural delivery while resorting to appropriate hematological treatment.

Fibrinogen Infusion

If tests in Stage 1 (Table 2) indicate a fibrinogen deficit, fibrinogen infusion may be indicated. The dose to be given should be calculated to bring the patient's fibrinogen level up to 3 Gm./liter. About 15 minutes after the infusion the plasma concentration should again be determined, and about every two hours thereafter. There is about a 5% chance of homologous serum hepatitis developing in patients receiving fibrinogen. There is also a definite danger of aggravating fibrin deposition which is a factor in so many of these cases. The concomitant use of heparin to avoid this hazard will be discussed later.

Fresh Plasma

If Stage 2 tests (Table 2) suggest the presence of a thromboplastic factor deficiency, either congenital or acquired in the defibrination process, and if fibrinogen has failed to control bleeding, then whole fresh plasma should be given. One liter of fresh plasma should be given as a rapid infusion. This dose may be repeated twice a day if necessary.

Platelet Transfusion

Platelet transfusions may be used if the platelet count is under 100,000 and surgery is contemplated; but it is not necessary to use platelet transfusions if delivery is to be natural. Thrombocytopenia *per se* does not increase the risk appreciably in natural delivery.[13] Fibrinogen concentration should be 200 mg./100 cc. plasma and factor VIII levels adequate to ensure an uneventful spontaneous delivery.

Heparin Therapy

The results of heparin therapy in patients with defibrination has been gratifying. Platelet counts and fibrinogen levels have risen and bleeding has stopped when heparin has been given, only to recur when heparin was discontinued.[15,16] The presence of fibrinolysin activity cannot be construed as a contraindication to heparin, since the fibrinolysin is probably a secondary phenomenon, and it is doubtful that any further harm can accrue by the addition of heparin to a patient whose blood is not clotting. However, if any increased bleeding appeared to follow, the heparin could be quickly neutralized with protamine. Heparin should be used early along with replacement therapy of deficient blood factors in the defibrination syndrome. A method of calculating the dose of heparin based on the platelet count has been proposed by Bernstock and Hirson.[17] This entails dividing the platelet count by 50. For example: a patient with a platelet count of 100,000 would be given 2000 units of heparin intravenously, repeated every four hours. Platelets seem to exert some inhibitory effect on the effect of heparin.

Epsilon amino caproic acid is an effective inhibitor of fibrinolysin, but the appropriateness of its use in the defibrination syndrome without heparin is open to question. Definite cases of thromboembolism following its use have been documented.[18] Epsilon amino caproic acid has been shown to cross the placental barrier and therefore should be avoided in the immediate prenatal period.[19] When infused into the mother, epsilon amino caproic acid is able to inhibit fibrinolytic activity normally found in the newborn, an action which raises a serious possibility in view of some studies which would attribute hyaline membrane disease to failure of fetal fibrinolysis. Epsilon amino caproic acid is able to block the reticuloendothelial system. In view of data already presented on the Shwartzman phenomenon, this may represent a serious threat in the patient with defibrination. Perhaps the only clear-cut indication for epsilon amino caproic acid alone is in fibrinolysis seen in prostatic surgery. If one feels disposed to use epsilon amino caproic acid in defibrination syndromes because of an active fibrinolysin, it would seem appropriate to administer heparin also.[20] The usual dose is 4 Gm. in the first half hour followed by 1 Gm./hour for 12 hours, given intravenously.

Protamine may be indicated in certain cases where heparin-like activity seems prominent. A dose of not greater than 200 mg. may be given intravenously and repeated after one hour if necessary, preferably monitored by protamine titration. Excessive doses of protamine have an anticoagulant effect produced by binding with factors V and VIII. This takes place after heparin, which it binds preferentially, has been neutralized by protamine.

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14-20 May be secured from the author or the reprints.

Derivatively Speaking

Alcohol: from Arabic al-kuhl, a powder for painting the eyelids.

Operation Longevity

How should one live in order to reach a great age, free of diseases and breakages, and what hints can we learn from nature? Many recipes have been offered to the eternally optimistic human race. Centenarians have been asked how they spent their days. If one of these Nestors* replied that he had drunk wine mixed with honey every day, it was believed that an *elixir vitae* had been found. If another said that every evening he went to bed at the same time as the chickens, and poured ice-cold water over himself every morning, it was believed that this was the golden rule for life. Gorgias, who reached the age of a hundred and nine, replied to the question of how he had reached such a great age: "Because I have accepted as few invitations as possible to drinking sessions." Petrarch, too, remarks in his De Consolatione: "More men die from eating and excessive drinking than from the sword, and he who leads a moderate life will live to a ripe old age." Vegetarians think that they possess the key to health and longevity in their diet, the followers of Mazda in the strict eating of raw food and breathing exercises. It is impossible to list all the recipes and theories which have been put forward, and we confine ourselves here to dealing with two, on account of their originality:

Metschnikoff noticed that among the Bulgarian peasants there were more than two thousand centenarians. Investigating their way of life he discovered that they all drank large quantities of their national beverage, yoghourt. "Death resides in the bowels!" he declared. "We age as a result of the poisonous bacteria in our gut. The man who drinks yoghourt disinfects the bowel and will have a long life." For twenty years Metschnikoff obstinately tried to prove the validity of his hypothesis. He avoided alcohol and did not smoke; he examined his faeces daily for pathogenic bacteria and drank pints of yoghourt, although his palate yearned for something more spicy. He led a pathetic life in the cause of hygiene, but the results were meager—he died at the age of seventy-one.

If this experiment contained a grain of sense and logic, with a good prospect of success, the following undertaking is off the beaten track and peculiar. About 1880, Gustav Jaeger, an outstanding zoologist, advanced the theory that in order to remain healthy and attain a ripe age one must wear underclothes of animal fiber. The basis of his theory was as follows: "In the case of an animal, the excretions of specific odorants cause emotional disturbances, urges and instincts, and probably the formatory powers of the body and mind. The same thing presumably applies to human beings. But whereas with the animal these odorants are preserved in the pelt, they become weakened in man by porous clothing and are lost. This loss causes body and mind to wither and age. Wool like the pelt of an animal is capable of preserving these important constructive and forming materials. In this way body and mind remain healthy and fresh." Jaeger did not provide future generations with an experimental proof of his theory, or of the efficacy of Jaeger undergarments.**

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*See Test Your Word Score Page 217.

**H. S. Glasscheib, M.D.: The March of Medicine, 1964.

The great tragedy of science—the slaying of a beautiful hypothesis by an ugly fact.—T. H. Huxley

Artificial Heart

II—Application of Nonpulsatile Radially Increasing Pressure Gradient Pumping Principle*

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Background

THIS LABORATORY group has been conducting investigations into the suitability of nonpulsatile pumps in connection with the development of an artificial heart. One such pump, utilizing the force-vortex# principle of pumping, exhibited high efficiency and a remarkable capability for circulating blood at high flow rates without damage to the blood elements.[1] In an extension of the study of that type pump, lifting surface conveying channels were added to the basic unit. The findings recorded from studies carried out on the modified pump form the basis of this report.

Description

The nonpulsatile pump operates on the principle of radially increasing pressure gradients. Due to the extreme gentleness with which the force-vortex pump handled blood it was felt that it might be possible to trade off some of the qualities of atraumatic handling of the blood for increased efficiency. To accomplish this objective, lifting surface conveying channels were inserted into the basic force-vortex pump unit (Figure 1). These channels served to lift the fluid from the center of the shaft and quickly accelerate it out to the surrounding pump head space. The performance characteristics of this pump basically conform to Bernoulli's equation.

Methodology

The methodology was essentially the same as that carried out in the case of the force-vortex pump tested by this group,[1] and the same hematological studies were performed. The in-vitro circulation of blood in a semi-closed system was carried out at shaft r.p.m.s between 425 and 875. Pump efficiency determinations were made in the same manner as for the force-vortex pump.[1]

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*See Part I, Minnesota Med 51:11, 1968.
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#See Test Your Word Score Page 217.

Results

Pump efficiencies in the order of 50% were obtained.

Figure 2 shows graphically the various flow rates and pressure heads attained at various r.p.m.s with water as the circulating fluid and with an input pressure of zero. Similar flows and pressures were achieved at a given r.p.m. when blood was substituted for water as the circulating fluid.

Continuous circulation of blood was maintained for six hours. Samples of blood were periodically taken from the reservoir for analyses. During these tests no hemolysis was detected by serial plasma hemoglobin determinations. No destruction of blood elements was detected during the period of circulation. A study of the platelets at the conclusion of the run revealed them to be normal in appearance and numbers. Defibrinization of the blood did not occur. Neutralization of the citrate effect with calcium chloride at the conclusion of the six-hour period of circulation resulted in prompt clotting of the blood (2½ minutes). Blood collected from the system at the completion of the run exhibited clot retraction of normal quality and time.

Discussion

The nonpulsatile pump described is one operating on a radially increasing pressure gradient pumping principle. This pump exhibits high efficiency in terms of converting mechanical energy into fluid flow. Additionally, it is atraumatic to blood. This model represents another type of nonpulsatile pump in a

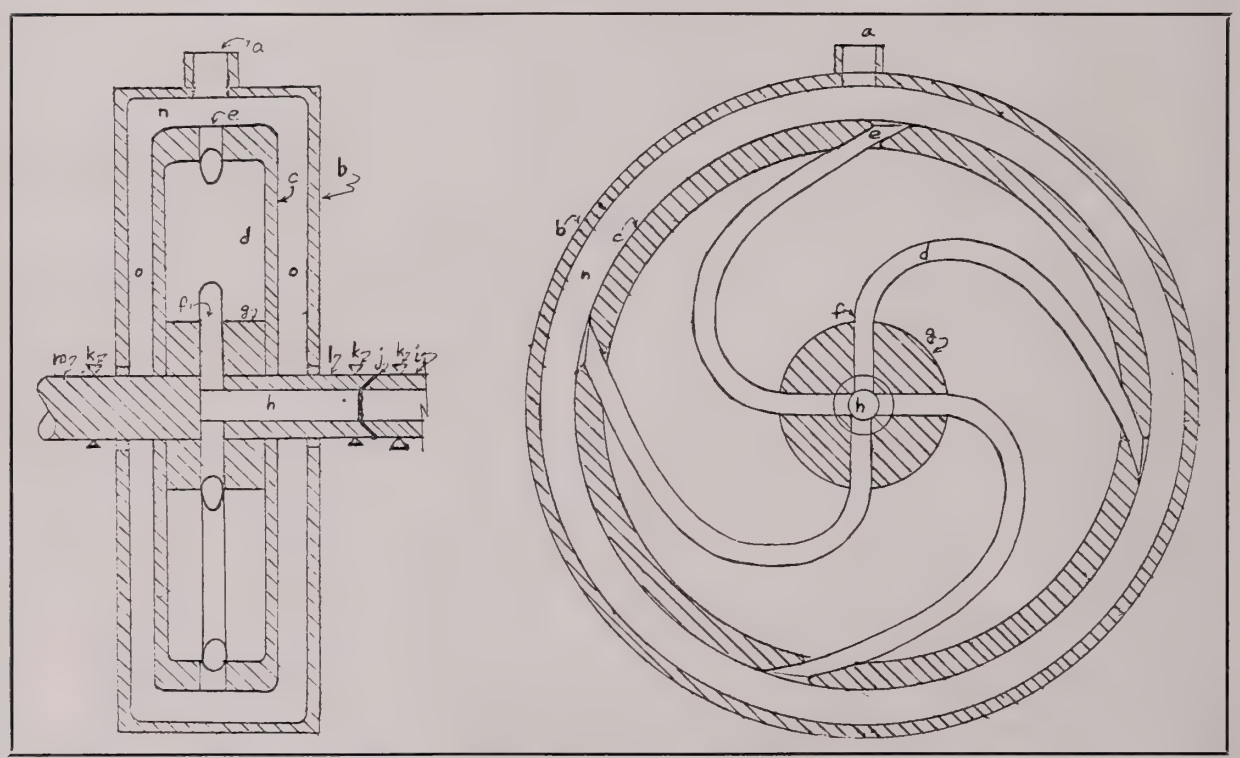


Fig. 1—Schematic cross-section of artificial heart: (a) pump outlet, (b) pump housing, (c) rotator, (d) rotator chamber, (e) rotator outlet, (f) rotator inlet, (g) shaft-to-rotator connector, (h) pump inlet, (i) stationary teflon inlet, (j) teflon-to-teflon seal, (k) bearings, (l) rotating inlet shaft, (m) stainless steel pump shaft, (n) head space, (o) side space. Plexiglass was used as the construction material for a, b, c, and g.

Dimensions:	
External diameter, rotator	8½"
External width, rotator	1¾"
Internal diameter, pump housing	11⅛"
Internal width, pump housing	3¼"
Internal diameter, teflon inlet	½"
Internal diameter, pump outlet	½"
Outlet and inlet diameters, rotator	⅜"

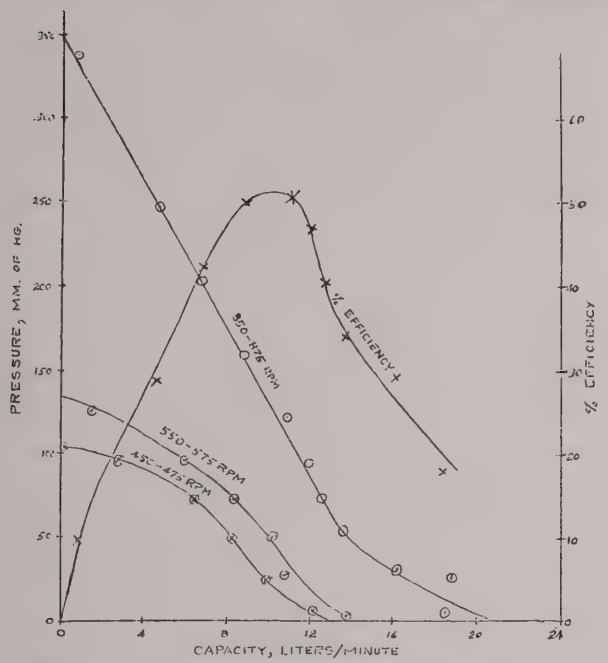


Fig. 2—Capacity vs. pressure and % efficiency.

continuing effort to optimize the performance of such units.

Although with this pump a slightly greater output was obtained when compared with the force-vortex pump, neither design necessarily represents that which will ultimately furnish optimum performance attainable for each given pump. In fact, it is probable that the design was not optimum, since design of the unit was tailored to ease of construction, visual testing capability, and ease of adaptability to testing modifications. Information obtained on stroboscopic study of fluid flow characteristics in the force-vortex model indicates that the curvature path preselected for the conveying channels in the modified pump was in retrospect of suboptimum design for gentlest handling of the fluid. Improvement in performance in this regard should follow a correction of this design feature.

As in the case of the force-vortex pump, blood utilized for testing the current pump was pooled from unfasted sick dogs.

Conclusions

A nonpulsatile pump operating on a radially increasing pressure gradient pumping principle has been described. This pump performed at high efficiency and was atraumatic to blood despite suboptimally designed conveying channels. As anticipated, an increase in efficiency of this pump over the force-vortex pump was obtained. For the period tested and with the particular tests employed, there was no detectable increase in trauma to the blood. Because of these favorable characteristics, continued studies are in progress to optimize such a unit for eventual use as an artificial heart as well as for extracorporeal uses.

Acknowledgments

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Tradition is but a meteor, which, if it once falls, cannot be rekindled.—Memory once interrupted, is not to be recalled.—But written learning is a fixed luminary, which, after the cloud that had hidden it has passed away, is again bright in its proper station.—So books are faithful repositories, which may be awhile neglected or forgotten, but when opened again, will again impart instruction.—Johnson

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Truth on Two Legs

It is good to express a matter in two ways simultaneously so as to give it both a right foot and a left. Truth can stand on one leg, to be sure, but with two it can walk and get about.—Nietzche

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There is more felicity on the far side of baldness than young men can possibly imagine.—L. P. Smith

Mr. President—Your Health*

Rutherford B. Hayes (1822-1893)

Any American doctor advocating moderation and equanimity to a patient can point with national pride to Rutherford B. Hayes, the Republic's nineteenth President.

Never husky, yet healthy and athletic, young Rutherford hunted, hiked, fished, swam, and skated—on one momentous occasion breaking through the ice. It was in this predicament that he demonstrated his innate composure by not struggling or panicking but serenely waiting to be rescued.

At college he went in for track, also bare-handed baseball until, after injuring several of his fingers, he decided that the sport of gloveless baseball was not for him but had best be left to juveniles. His hiking endurance and capacity were once ruggedly demonstrated by his walking home from college forty miles in twelve hours through four-inch-deep snow.

When a young practicing lawyer in his twenties Hayes suffered from frequent sore throats, an affliction finally culminating in an attack of quinsy, which was treated and apparently cured by rest, cathartics, and codliver oil.

While he was serving as a colonel in the Civil War at the Battle of South Mountain, Hayes' left arm was fractured by a bullet. After a comrade had stanched the hemorrhage that followed, Hayes struggled to his feet to continue fighting, but collapsed and had to be carried off the field. Later, in an engagement at Fishers Hill and Cedar Creek, his horse was shot out from under him and his ankle painfully wrenched. Undaunted, he promptly mounted another steed and heroically proceeded into action from where he had left off. Nor was this the only time his horse was shot out from under him! On three more occasions enemy fire brought down his mount—without disturbing its rider's magnificent aplomb.

In his middle years as a Representative from Ohio, Hayes was a handsome man with perfect teeth and vision so good as not to require glasses, an anomaly doubtless due to early myopia offset by later presbyopia. He maintained superb physical fitness by daily setting-up exercises and brisk walks. In his pursuit of the Greek ideal of moderation he drank coffee and tea very sparingly; from tobacco and alcohol he abstained completely.

As President, Hayes continued his schedule of exercise and his practice of moderation, permitting himself only one cup of coffee for breakfast and one cup of tea with his lunch.

Even after retirement Hayes became neither complacent nor careless in his habits but meticulously maintained the straight and narrow path he had resolved on. He never kept late hours, preferring to retire before inside illumination was required.

Nevertheless, in Hayes' late sixties age began to creep up on him—with mild but progressive evidences of irreversible deterioration: impaired memory and hearing and diminished vigor and agility. Of his aging, however, it can well be said: Time alone was the pen!

In early January 1893 Hayes contracted a severe cold with a cough, followed in a few days by acute chest pain and shock. Two weeks later, while confined to his bed under sedatives he suffered a coronary thrombosis which terminated his life, at the Biblically allotted years of three score and ten.

*With acknowledgments to Karl C. Wold, M.D.: Mr. President—How Is Your Health?

Critique of the Provocative Intradermal Food Test*

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"Food allergy has been recognized as a cause not only of gastrointestinal symptoms, but also of a variety of functional disorders, including asthma, allergic rhinitis, urticaria, angioedema, eczema, migraine, and other bizarre syndromes."[1] The diagnosis of food allergy, however, has often been difficult or tedious. "Skin tests for foods are held in low esteem because of so many cases where a positive test was not confirmed clinically, or where a negative test occurred with certain clinical evidence of allergy to that food. Many allergists disregard the results of skin tests with foods, and some have discontinued skin testing with foods, depending rather on clinic trial-and-error diets, elimination diets, or intentional-feeding diets."[2]

With such a situation existing, then, it was noteworthy when the provocative intradermal food test was proposed.[3] The provocative injection of solution of food extract would provoke or elicit the same symptoms to a small degree that the food caused when ingested. The size of the skin reaction was not significant. The symptoms would then be relieved by a higher dilution of that food extract, called the neutralizing dose. Later papers[4,5,6] confirm the reliability and safety of the procedure. Although I have not found any reference in the literature claiming this test to be unreliable or impractical, some allergists may regard it as controversial. Therefore, an evaluation of patients tested by this procedure seems in order if the field of medicine is to continue to progress. Because there is a great need for an accurate simple quick method of diagnosing food allergy (or idiosyncrasy or intolerance or hypersensitivity or reaction) a procedure such as the provocative intradermal food test should be either confirmed and upheld, or refuted and discredited. It certainly should not be ignored.

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*Presented at the North Central Allergy Society, Madison, Wisconsin, May 6, 1967, and at the American Association for Clinical Immunology and Allergy, Las Vegas, Nevada, November 28, 1967.

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Methods of Study

With this in mind, I present cases of positive reaction to one or more foods by the provocative intradermal food test. To avoid the factor of suggestion, the patient was not allowed to know which food was being tested, nor whether a particular injection was expected to provoke or exacerbate or relieve a symptom, or to have no effect. A detailed food allergy or intolerance history was obtained in every case; symptoms were noted as to whether they were associated with eating of a food and cleared with avoidance of that food, and also whether they recurred with resumption of that food in the diet. Thus specific food allergy, elimination, and intentional feeding were studied in relation to the findings of the provocative intradermal food test.

(In my series the provocative dose was 0.05 cc. of 1:5 dilution of a commercial 1:20 food concentrate—#1 dilution—waiting for 10 minutes for appearance of symptoms, and if no change a four-minute wait for symptoms after a subsequent injection of 0.02 cc. of 1:125 dilution of that concentrate—#3 dilution.)

TABLE 1

Diagnoses in 100 Patients with Positive Reactions to Foods.

Presenting Diagnosis	Number of Patients
allergic rhinitis	41
gastrointestinal syndrome	19
bronchial asthma	15
allergic dermatitis	14
headache	11
urticaria	11
allergic conjunctivitis	4
allergic bronchitis	3
allergic Eustachian salpingitis	3
fatigue	3
colitis	2
allergic pharyngitis	1
angioedema	1
arthralgia	1

TABLE 2

Comparative Frequency of Foods in Positive Test Reactions Confirmed by Diet in 95 Patients.

Food	Number of Patients
milk	48
corn	41
wheat	38
egg	27
beef	15
potato	14
coffee	11
lettuce	8
pork	7
orange	5
tomato	4
chicken	2
yeast	2

TABLE 3

Number of Food Sensitivities in These 95 Positive Reactors.

Number of Foods	Number of Patients
one	33
two	28
three	20
four	9
five	2
six	2
seven	0
eight	0
nine	0
ten	0
eleven	1
Total	95

Results

This series of positive reactors consisted of 110 patients. Four failed to follow their diet, so could not confirm or refute the accuracy of the findings of the provocative intradermal food test. Six were lost to followup. Of the remaining 100 patients, in 86 the symptoms cleared on avoiding the offending food and recurred again on eating the food. In nine the symptoms improved but did not clear completely on avoiding the offending food, but worsened considerably again on eating the offending food. Thus the provocative intradermal food test confirmed the dietary identification of the specified food responsible for the symptoms in 95 out of 100 cases (95%). The presenting diagnoses of these 100 patients are given in Table 1.

Milk, Corn and Wheat

Among the patients in whom the symptoms cleared or greatly improved on avoiding the specific food in their diet, milk was the most frequent allergen (48 patients), corn the next most frequent (41 patients), with wheat a close third (38 patients). Thirteen foods were found to be allergenic in this series. See Table 2.

Multiple Foods

Among those 95 patients who benefited by following their allergen-free diets, the number

of foods found to react by the provocative intradermal food test in each patient varied from one to eleven. One patient with urticaria who reacted to both wheat and egg by the tests stated later that on these occasions her hives cleared on avoiding eggs and recurred on eating them, but that she noticed no difference in her hives whether she ate wheat or avoided it. One 10-year-old patient with reactions to milk and corn confirmed this result with milk but failed to confirm it with corn. Whether he and his mother succeeded in having him follow a truly corn-free diet consistently is not certain. Because corn is present in some 130 foods in the form of corn oil, corn starch, corn sugar, or corn syrup, it is by far the most difficult to avoid.[7] One woman with allergic rhinitis confirmed potato, beef, and corn but not wheat. See Table 3.

Contradictory Observations

An evaluation of those five cases where the elimination diet failed to improve or relieve the symptom and the intentional-feeding diet failed to induce the symptom reveals no obvious common factor. The order of testing of the provocative food and the neutralizing dose was different in each of the five cases. The provocative food was different in each. The sex and ages differed. The presenting diagnosis or chief complaint differed: two had allergic rhinitis, one urticaria, one ulcerative colitis, one nonspecific gastrointestinal symptoms. See Table 4.

The most plausible explanations as to why the testimony of these five patients contradicted the findings of the clinic testing are three:

Another Factor Contributed to the Symptoms.

Two patients were also allergic to house-dust; one had phlegm in her throat as the provoked symptom; the other had an increase in her postnasal drip, both common symptoms of house-dust sensitivity.

Inaccurate Reporting

One patient denied relief of stomach pressure and pains and borborygmi from avoiding corn (if he actually did avoid all forms of corn completely) and denied worsening of symptoms with eating corn, yet he stated he got enough relief from corn propetans[8] to request a refill when his supply was used up!

Coincidental Symptoms.

One would suspect that a symptom occurring after the provocative dose might be coincidental, especially if it occurred only once and was very mild, e.g., *one* scratch, *one* cough, or *one* burp. It may be that I misinterpreted the significance of the symptoms. Such symptoms as burping, scratching, and coughing were actually counted and recorded as to time during both control periods and test periods; a positive result was called only when there was a decided increase in symptoms during the test period as compared to the control periods before and after. A frank attack of bronchial asthma was not elicited by any test; at best barely audible wheezing and increased respiratory excursion were observed. This would be expected, since the symptoms provoked are symptoms "in miniature."

The patient may have failed to eat the offending food within the preceding four days.

Value of Provocative Testing

Negative Results

Is a negative result reliable? The data on those patients who had only negative findings were collected; only 25 cases were found whose allergenicity had been suspected. Of those 25, 23 confirmed the negative tests by failing to show relief of symptoms on avoiding a suspected food, and failing to show worsening of symptoms on eating that food. Two did give a history of food intolerance confirmed by diet manipulation. The first was a 35-year-old male with ulcerative colitis, who declared he got indigestion from milk; the second was a 79-year-old male with complaint of burning urine, who declared his urine burned whenever he drank coffee. Yet no symptoms

TABLE 4

Data on Five Patients Whose Positive Tests Were Contradicted by Diet Trials.

Age, Sex	Diagnosis	Prior Symptoms	Positive Reactors	Order of Food Tested	Induced Symptoms
53 f	all. rhin.	yes	coffee	fourth	phlegm in throat, clearing throat, hawking
64 f	all. rhin.	yes	milk	first	more postnasal drip
28 f	urticaria	yes	egg	second	itch (one hive appeared)
29 m	ul. col.	no	orange, wheat	second, sixth	full feeling, abdominal cramp, burp
40 m	G. I.	no	corn	third	pains in abdomen, borborygmi, pressure in stomach

were elicited by the provocative intradermal food test for milk in the former, or for coffee in the latter. Although 25 cases is a small number from which to draw conclusions, they do suggest that this test is about 92% accurate, in ruling out a specific food allergy.

The ages of the patients are shown in Table 5. To give the reader an idea of how thorough or incomplete the testing was, the number of foods tested on each patient is given in Table 6.

TABLE 5
Ages of Patients

Age Group	Number of Patients
1-10	2
11-20	22
21-30	21
31-40	28
41-50	24
51-60	21
61-70	11
71-80	6
Total	135

TABLE 6
Number of Foods Tested on Each Patient in all Groups.

Number of Foods Tested	Number of Patients
one	10
two	7
three	10
four	14
five	23
six	19
seven	17
eight	13
nine	12
ten	5
eleven	3
twelve	0
thirteen	2
Total	135

Otorhinolaryngological Cases

The provocative intradermal food test is of most value in otorhinolaryngological cases, since a large number of cases of food allergy have as their symptom increase in mucin production, noted by the patient as formation of phlegm in the nose and throat. In the present series 63 of the 100 patients had symptoms referable to the eye, ear, nose, or throat. This may explain why the ear-nose-and-throat specialists use this test more widely than do the internal medicine and pediatric allergists.

Diagnostic Advantage

This technique for diagnosis of food allergy has several advantages. (1) It is more accurate than skin tests for foods measured by local skin reactions, which "are dependable in less than 50% of the cases."[9] (2) It is more informative; it not only demonstrates a reaction to the food but shows what symptoms that food produced. (3) It gives the answer in one clinic visit, not after many days, such as the elimination diet and intentional feeding require. (4) It eliminates the diagnostic necessity of following a rigid, difficult, restrictive diet without respite day after day, a tedious demand that very few patients have the ability, motivation, or will power to pursue. (5) It is safe; I have never had a serious reaction to one of the injections, but I have never tested for a food which has already been proven to cause a severe reaction, and I do not recommend testing in such a case. (6) It provides another worthwhile method of diagnosing food allergy.

Disadvantages

This method of testing for food sensitivity has several disadvantages, however. (1) It is slow; with the technique used a minimum of 10 to 14 minutes is required for each food, and only one food at a time can be tested, unless one is screening. If several foods are tested at the same time and a positive response is obtained, each food must then be tested individually. (2) It is tedious and demanding; one must watch the patient constantly with no interruptions for as long as the test runs. If not, symptoms will be overlooked and a false negative report will result. (3) It is difficult to interpret as it is sometimes uncertain whether a trivial symptom is due to the injection or is coincidental. Measurement of symptoms and degree of lessening or worsening must be inexact because of the subjective nature of the process; degree of response may vary, just as in allergic rhinitis or bronchial asthma on different occasions upon identical exposure to an inhalant. The method is necessarily highly subjective because the test elicits symptoms. Placebos were used to test foods to which the patient was not expected to react because of negative history of intolerance to that food.

A double-blind method was not feasible, since I had to determine which foods were suspect by history, then test for these foods. (4) It requires intelligent cooperation on the part of the patient. If the patient fails to inform the physician of the occurrence of a symptom, or cannot discern a change in his psyche, a significant symptom will be missed. (5) The patient must have been off anticholinergic, antihistaminic, and sympathomimetic drugs for at least 1½ days (and, ideally, steroids for a longer time); but this is also true with scratch and intradermal tests. (6) The patient must have eaten the offending food within the last four days to yield a positive test.

Comments

The results of correlation of test findings with diet findings are summarized in Table 7.

TABLE 7
Summary of Results

		DIET	
		+	−
P.I.F.T.	+	95	5
	−	2	23

After avoiding the offending food for a long enough time, the patient usually loses his sensitivity to it; thereafter, eating it—at least in moderation—produces no symptoms. At this stage he is apt to disbelieve he ever was allergic to it.

It is not evident that food allergy patients represent truly atopic* individuals; in fact, there is more evidence that they do not. The rare patient who reacts anaphylactically to nuts or seafood probably is an "atope," but this type of patient wasn't studied. The great majority of patients with intolerance to food do not have atopic histories and have shown no reagins in their skin or food antibodies in their serum and do not readily demonstrate eosinophilia with a delayed reaction to the food. Some allergists wish to restrict themselves to reagins; if they do they will not concern themselves with the bulk of food allergy. Food allergy is a very controversial area; for this reason it is imperative that techniques like the provocative intradermal food test be studied and discussed, not neglected.

*See Test Your Word Score Page 217.

Summary

1. The findings on diet manipulation by elimination and intentional feeding were compared with the results of the provocative intradermal food test, to evaluate this test's accuracy.

2. In 100 cases giving positive tests 95 patients substantiated these by showing alleviation of symptoms on avoiding the specific food, and recurrence on resuming the food. This would indicate a 95% correlation between the two methods of diagnosing food allergy.

3. In 25 cases giving negative tests 23 failed to show a change in symptoms whether they did or did not eat each food giving a negative test. This would indicate a 92% correlation.

4. The provocative intradermal food test has certain advantages and disadvantages but is nevertheless a worthwhile addition to the practitioner's diagnostic methods. The results must be accepted with caution, however, for unless one becomes an expert he should double-check the results by other means, such as by diet manipulation.

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Truth

He who does not know truth at sight is unworthy of her notice.—Blake

Beckie

Not that I never made mistakes. There was Beckie, for instance. Probably every hospital has its oddities, but among those at Gouverneur Hospital in my day, Beckie easily led the list. She was a character Balzac might easily have written about. Beckie was our prima donna of malingerers, and don't think that I am telling you about any ordinary performer. No indeed! She had a method and technique so unique and productive of results that she fascinated us all. When the outside world got too cruel she knew how to enter a hospital and secure the best skill and attention, food, and shelter.

Beckie believed in the dramatic and when she decided that the time had come for another hospital sojourn, she would invariably pick out a street corner where there was plenty of room for a sympathetic crowd to gather, and gather they always did. She would have to decide what ailment to fake.

It must be remembered that methods of diagnosis were more primitive then, and lacking all the tests of later days, greater reliance had to be put on the patient's own testimony. On one occasion I was told she had produced indications of acute appendicitis so convincing that an immediate operation was performed, and rumor hath it that it was none other than John F. Erdmann himself who removed a perfectly normal appendix. This, however, was before my time.

Was it surprising then that, in spite of the reputation of this malingerer, I, a green young doctor, should not have spotted Beckie when it was my turn to be called. I found the usual crowd, surrounding a pathetic little woman writhing apparently in death agonies. She seemed to have a great tumor mass in her stomach region suggesting an intestinal obstruction. I didn't even think of considering that her symptoms might be feigned, through some power to control and contract muscles in an unusual way. Instead the patient got at once my best care and was rushed to the hospital at top speed, put to bed immediately and with all the nurses on the service rushing with restoratives and sedatives for her pain. Immediately I reported this patient to my superior officer, and when he arrived he at once recognized Beckie, much to his glee and my discomfiture. However, Beckie was equal to the occasion and now that she was in the hospital with a good bed, food, and shelter, she did not intend to convalesce too rapidly.

Beckie took her time and several days elapsed before she allowed her phantom tumor to disappear. When finally she was ready for discharge, I believed she could stand some straight talk and I said to her: "Beckie, you know you are a wonderful fake. Now, if ever you throw a fit on a street corner again and I am on the bus, I'll arrest you and take you to the station house, not to the hospital. Perhaps you do not know it, but when I am on the ambulance, I am a Sergeant of Police."

Several months must have elapsed, and I had forgotten about Beckie, when one day an urgent hurry call came in. As we neared the scene of action the crowd parted to make room for the ambulance and leaning far out I made a quick survey of the situation before the bus had come to a stop. In those few seconds I caught the furtive eyes of Beckie and she knew perfectly well who I was. Before I could reach her she gave one mighty jump, and with the agility of a gazelle, began running in the opposite direction. As she fled she picked up speed and I doubt if any of the bluecoats on the police force could have caught her. She may be running still for all I know, for I never saw or heard of Beckie again while I was at Gouverneur Hospital.*

* Emily Barringer, M.D.: Memoirs of a Lady Ambulance Surgeon, Bowery to Bellevue, 1950.



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(8 monkeys in each group)

conclusion:

*Under the conditions of this study and the doses employed, it was found that

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was far superior to erythromycin, as was cloxacillin, a bactericidal agent, and of particular interest, "...bacteriostatic triacetyloleandomycin was as effective or perhaps superior to cloxacillin in preventing lethal (staphylococcal, phage type 80/81) infection."

*It should be pointed out that results obtained in an experimental study of this nature may not necessarily be directly extrapolated to the clinical situation as it pertains to man.

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INDICATIONS: Include streptococci, staphylococci, pneumococci and gonococci. Recommended for acute, severe infections where adequate sensitivity testing has demonstrated susceptibility to this antibiotic and resistance to less toxic agents. **CONTRAINDICATIONS AND PRECAUTIONS:** Not recommended for prophylaxis or in the treatment of infectious processes which may require more than ten days continuous therapy. In view of the possible hepatoxicity of this drug when therapy beyond ten days proves necessary, other less toxic agents should be used. If clinical judgement dictates continuation of therapy for longer periods, serial monitoring of liver profile is recommended, and the drug should be discontinued at the first evidence of any form of liver abnormality. When treating gonorrhea in which lesions of primary or secondary syphilis are suspected, proper diagnostic procedures, including darkfield examinations, should be followed. In other cases in which concomitant syphilis is suspected, monthly serological tests should be made for at least four months. Contraindicated in pre-existing liver disease or dysfunction, and in individuals hypersensitive to the drug. Although reactions of an allergic nature are infrequent and seldom severe, those of the anaphylactoid type have occurred on rare occasions. When used in streptococcal infections, therapy should be continued for ten days to prevent the development of rheumatic fever or glomerulonephritis. The use of antibiotics may occasionally permit overgrowth of nonsusceptible organisms. A resistant infection or superinfection requires re-evaluation of the patient's therapy. In the event such occurs with this drug the medication should be discontinued, and specific antibacterial and supportive therapy instituted.

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in children with . . . Gastroenteritis ▪ Spastic bowel
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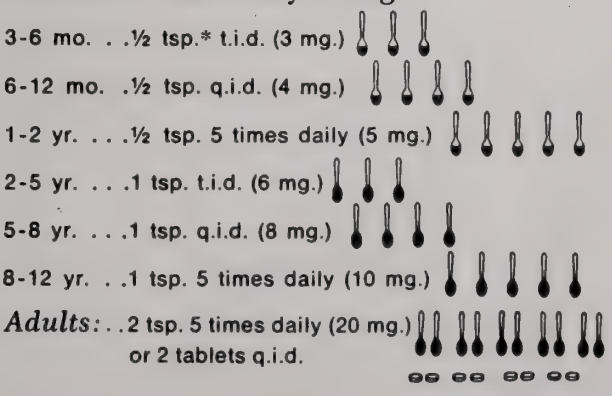
Precautions: Lomotil is a Federally exempt narcotic preparation of very low addictive potential. Recommended dosages should not be exceeded, and medication should be kept out of reach of children. Should accidental overdosage occur signs may include severe respiratory depression, flushing, lethargy or coma, hypotonic reflexes, nystagmus, pinpoint pupils, tachycardia; continuous observation is recommended. Lomotil should be used with caution in patients with impaired liver function or those taking addicting drugs or barbiturates.

Side Effects: Side effects are relatively uncommon but among those reported are gastrointestinal irritation, sedation, dizziness, cutaneous manifestations, restlessness, insomnia, numbness of the extremities, headache, blurring of vision, swelling of the gums, euphoria, depression and general malaise.

Dosage: The recommended initial daily dosages, given in divided doses until diarrhea is controlled, are:

Children: Total Daily Dosage

3-6 mo. . .½ tsp.* t.i.d. (3 mg.)
6-12 mo. .½ tsp. q.i.d. (4 mg.)
1-2 yr. . . .½ tsp. 5 times daily (5 mg.)
2-5 yr. . . .1 tsp. t.i.d. (6 mg.)
5-8 yr. . . .1 tsp. q.i.d. (8 mg.)
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*Based on 4 cc. per teaspoonful.

Maintenance dosage may be as low as one-fourth the initial daily dosage.

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When the agitated businessman goes to work...

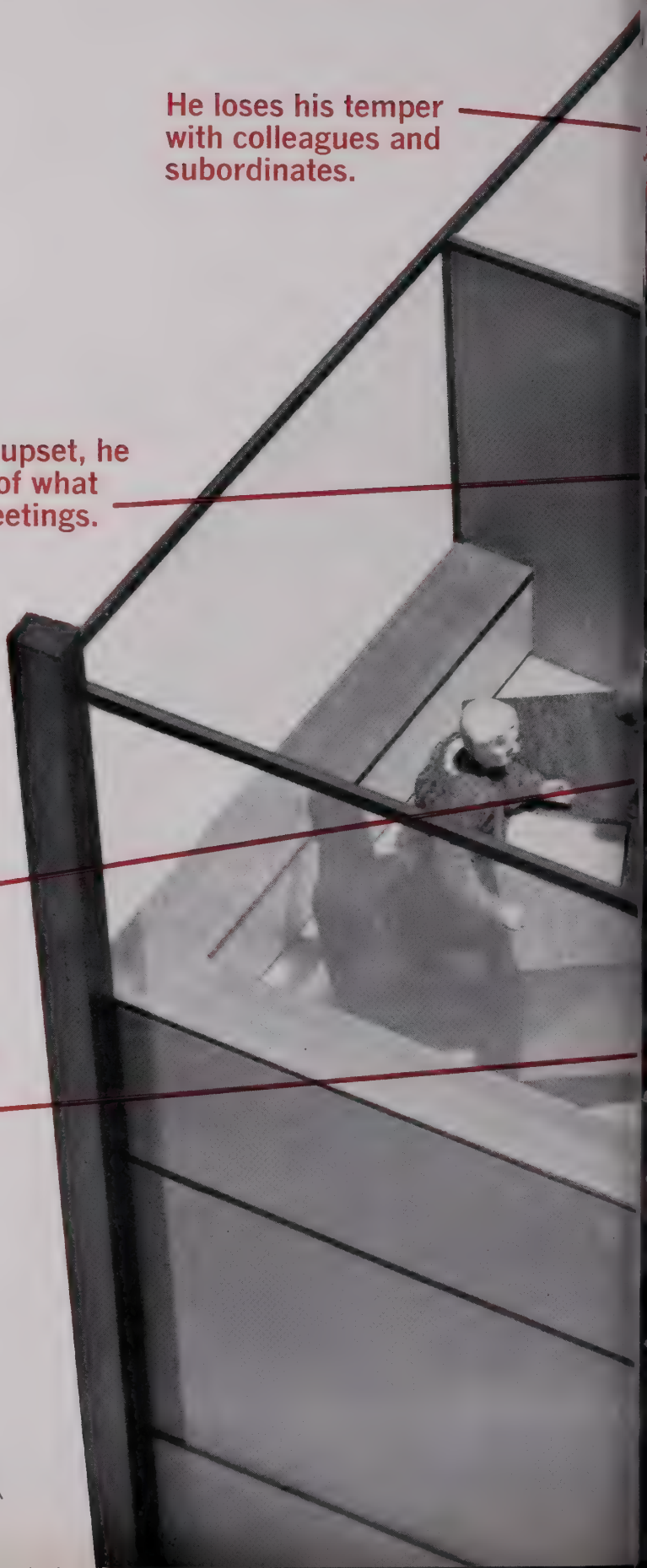
He goes home at night and takes it out on his family.

He loses his temper with colleagues and subordinates.

Emotionally upset, he misses half of what is said at meetings.

He is always fearful about his standing with the boss.

He just can't seem to settle down to his work.



for moderate to severe anxiety

Mellaril® (thioridazine) 25 mg. t.i.d.

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Anxiety that *seriously interferes* with the individual's performance at work, at home, or in the community may be regarded as *moderate to severe* in degree.

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Contraindications: Severely depressed or comatose states from any cause, and in association with or following MAO inhibitors; severe hypertensive or hypotensive heart disease.

Precautions: Hypersensitivity reactions (e.g., leukopenia, agranulocytosis) and convulsive seizures are infrequent. Pigmentary retinopathy has been observed where doses in excess of those recommended were used for long periods of time. May potentiate central nervous system depressants, atropine, and phosphorus insecticides. Where complete mental alertness is required, administer the drug cautiously and increase dosage gradually. In addition, orthostatic hypotension (especially in female patients) has been observed. Epinephrine should be avoided in treatment of drug-induced hypotension.

Side Effects: Pseudoparkinsonism and other extrapyramidal disorders are infrequent; drowsiness, especially in high doses early in treatment, may occur; nocturnal confusion, dryness of the mouth, nasal stuffiness, headache, peripheral edema, lactation, galactorrhea, and inhibition of ejaculation are noted on occasion; photosensitivity and other allergic skin reactions may occur but are extremely rare.

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Mellaril®
(thioridazine)
25 mg. t.i.d.

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Each tablet contains:

Potassium Iodide	195 mg.
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Editorials

Factors Influencing the Level of Lower Limb Amputations in Peripheral Vascular Disease

In recent years there has been a conservative trend in lower-limb amputation, as Dr. Kane* ably brings out in his article: *Factors Influencing the Level of Lower Limb Amputation in Peripheral Vascular Disease.* For the most part these amputations through the foot or the calf have provided the patient with a more usable limb than if the above-knee amputation had been done. Nevertheless, failures of these lower amputations to heal continue to occur, especially if there has been no improvement in circulation.

Reconstructive vascular procedures can be performed with less tissue destruction and less trauma to the patient than occur in a major amputation. The technique of venous by-pass grafting to the distal popliteal artery has been successfully extended to the anterior and posterior tibial arteries. When this level of good flow is accomplished it almost assures healing to the mid-foot level.

Although the vascular limb disease of diabetics is notable for the prevalence of endarterial obstruction, superficial femoral obstruction does occur; and if a diabetic develops ischemia from an obstruction to the superficial femoral artery he may well get a very satisfactory result from a by-pass graft and should not be excluded from a reconstructive procedure simply because he is a diabetic.

Finally, a femoral arteriogram to help determine whether a reconstructive procedure is possible can be performed with a very low incidence of complication by utilizing local anesthesia; and it should be done and evaluated on all candidates for amputations, excluding only those cases wherein the added length of limb salvage would be of no significant benefit to the patient.

Harrison H. Farley, M.D.
Minneapolis, Minnesota

*See page 179.

My books are water: those of the great geniuses are wine. Everybody drinks water.—Mark Twain

---

Any man whose actions leave his wife speechless really has hit on something.—Changing Times

Before prescribing, see complete prescribing information in SK&F literature or *PDR.* A brief precautionary statement follows.
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Complications of Bronchial Asthma

Intelligent symptomatic treatment of a patient with bronchial asthma involves an understanding of the underlying pathophysiologic processes. Management should be directed toward these primary processes—edema, bronchospasm, and tenacious secretions, along with their secondary consequences such as hypoventilation, dehydration and increased work of breathing. The therapeutic attack must also consider the complications resulting from these processes, such as pneumothorax, infection, atelectasis, subcutaneous emphysema and cardiac complications, as these may aggravate the primary condition and endanger the life of the patient.

Spontaneous development of mediastinal emphysema may be trivial or widespread. Two cases have been reported by David E. Dines and Gustavus Peters in the April issue of Minnesota Medicine.[1] As pointed out, this condition occurs more frequently than the medical literature indicates. Most of the cases reported occurred in patients whose asthma was of several years' duration. The outstanding sign is a peculiar, loud, crackling, bubbly sound synchronous with the heart beat. X-ray examination helps to confirm the diagnosis. Although mediastinal emphysema may result in severe respiratory distress and a shock-like state, it has not by itself been very serious in patients with asthma. This probably is because in the older child and adult the mediastinal air is decompressed rather easily into the neck and usually no pneumothorax develops. The average duration of this complication is between seven and 10 days.[2]

Complicating infections may play a major role in the prolongation of an acute attack of asthma. Infections need not be bacterial since mucosal edema and secretions due to viral disease may be just as harmful. It is therefore important to identify the causative organism.

Occasionally spontaneous pneumothorax is seen in patients with asthma. This condition is probably produced by the rupture of a bleb* from over-distension during an attack. In such instances, the patient is likely to have his breathing further embarrassed, and the condition may become serious. Because of the shortness of breath and the possible coexisting emphysema, the physical findings may be somewhat masked. However, careful physical examination showing the filled-out intercostal spaces, the enlarged chest wall, the tympanitic note, the absence of breath sounds and the displacement of the heart away from the affected side should be sufficient to make the diagnosis, which may be definitely confirmed by x-ray examination.

Spontaneous fracture of the ribs in asthma is rare. This usually results from violent coughing in which unusual muscular strain is applied to the ribs. Localized pain is a characteristic feature. Splinting because of the pain may aggravate the asthma.

Atelectasis is probably more commonly present than can be diagnosed. This complication may occur in asthma from the obstruction of a small or large bronchus by a mucus plug, following a general anesthetic or with a foreign body in a bronchus. Small areas of atelectasis must occur from time to time in asthma, giving rise to no apparent symptoms. When the plug remains for some time and there is an infection, bronchiectasis or pneumonitis may develop. The larger the area of atelectasis, the more serious is the condition. Onset may be sudden and the patient may become seriously ill. To compensate for the collapse of a whole lobe, the heart and mediastinum shift to the affected side and the diaphragm becomes elevated. This can be readily demonstrated by x-ray examination.

The relationship of heart failure and bronchial asthma is controversial. Certainly heart failure can be seen in elderly patients following the onset of asthma. Regardless of whether or not it is due to uncomplicated asthma the condition should be treated promptly. In addition to the above-mentioned complications, it must be remembered that people with asthma may have other diseases.

A patient with bronchial asthma should be treated with vigor—but cautiously. Complicating conditions in the asthmatic lung should be recognized and treated immediately, as they may be more important than the primary processes under consideration.

Malcolm N. Blumenthal, M.D.
Minneapolis, Minnesota

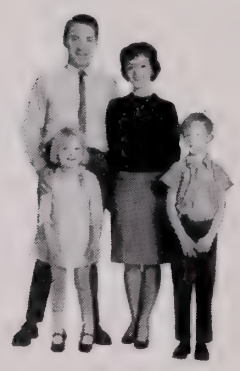
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*See Test Your Word Score Page 217.

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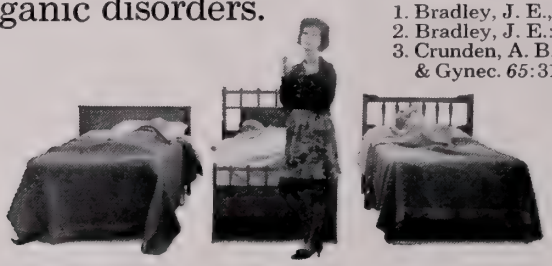
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1. Bradley, J. E., *et al.*: J. Pediat. *38*:41 (Jan.) 1951.
2. Bradley, J. E.: Mod. Med. *20*:71 (Oct. 15) 1952.
3. Crunden, A. B., Jr., and Davis, W. A.: Am. J. Obst. & Gynec. *65*:311 (Feb.) 1953.



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In cases of accidental loss of skin about the face, if the area can not be closed by undermining of the skin edges with direct approximation, application of a free skin graft to the open defect is indicated. If the avulsion is relatively clean or can be converted to a clean wound by debridement, primary closure of the defect with a free graft may be done. If the wound is jagged and viability of tissues is in question, debridement and dressing only, with secondary closure by grafting five to ten days later, is preferable.

*See Test Your Word Score Page 217.

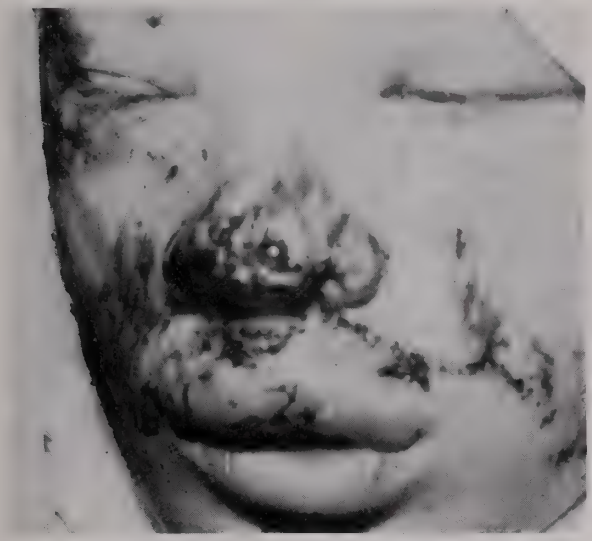


Fig. 1—Avulsion of 3 × 4 cm. area of skin over the tip and left side of nose. A thick split-thickness skin graft, taken from the clavicular region, was applied to cover the loss.



Fig. 2—Photograph nine months after accident. There is a good color match between the nasal skin graft and the surrounding nasal skin.

Full-thickness grafts attach poorly to facial wounds that are infected, whereas split-thickness skin grafts will attach more often. However, split-skin grafts taken from the abdomen, hip or thigh area match the facial skin poorly and appear as a conspicuous patch. After the wound has been healed by use of a thin graft, this conspicuous graft can later be removed and a thicker graft of better color match applied. This would then be applied on a freshly excised area and a good acceptance of the graft would be anticipated.

Ideally, if a thicker graft with a good color match could be applied at the time of initial repair, much time and expense could be saved. In selected cases, this can be done satisfactorily.

In case of loss of skin about the nose, face or ears, a good color match of the graft with the adjacent facial skin can usually be obtained if the graft is taken from an area close to the face. Two convenient donor sites are present: the postauricular sulcus region and the area about the clavicle.

A full-thickness graft can be cut free hand from the postauricular sulcus, and, with care, the graft can be cut even thinner than full thickness. A graft as large as 2.5 × 3.5 cm. can be taken from behind the ear and the defect closed primarily with sutures. A skin graft can be taken from the area below the clavicle, either as a full-thickness graft with primary suture closure of the wound, or as a thick split-thickness graft taken with a mechanical dermatome.*

If the area of skin loss is relatively small (3 × 4 cm. or less) and, more important, if the wound is clean and of recent origin, a full-thickness graft may be employed as an emergency but definitive procedure. The wound should be thoroughly cleansed, tissue shreds debrided, and hemostasis obtained before application of the graft. If the general condition of the patient is not satisfactory, grafting should be deferred; but since this can be done

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* anticostive, *adj.* (*anti* opposed to + *costive* causing constipation.) Against constipation. (Now isn't that a good idea in an iron-containing hematinic?)

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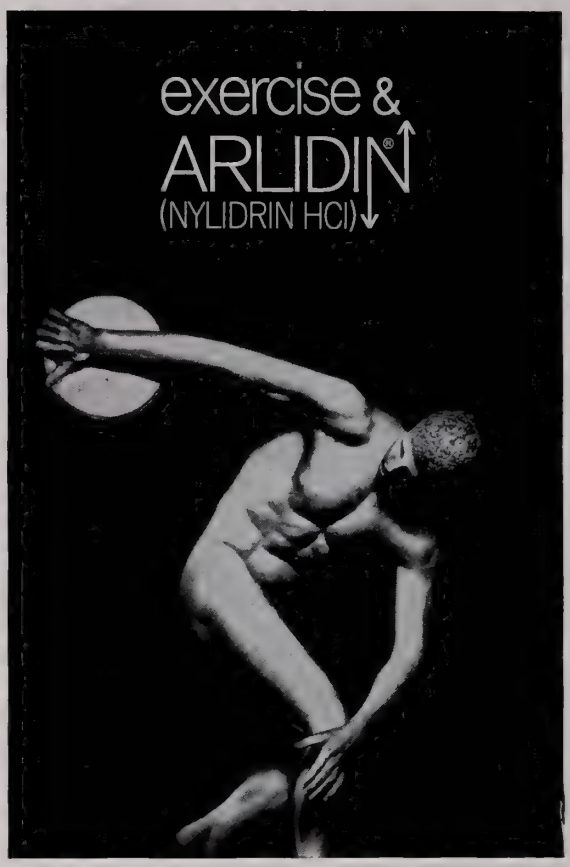
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under local anesthesia, it often can be employed in rather seriously injured individuals.

A pattern is obtained of the skin defect which needs graft coverage. This pattern is used for cutting the correct size graft (clavicular or postauricular). Following excision of the graft and careful removal of any fat along its raw surface (graft should be trimmed as thin as possible with sharp iris scissors), it is sutured over the defect using 5-0 silk sutures. The sutures are left long and are used to tie a bolus type dressing in place over the graft. This dressing will provide immobilization of the graft for the first five to seven days of healing.

In selected cases, application of a well-matched full-thickness skin graft can be applied to areas of facial skin loss as an emergency procedure. The author has observed attachment of the graft to be satisfactory and has found that the definitive graft application has saved considerable time and expense for the patient.

Lyle V. Kragh, M.D.
Minneapolis, Minn.

A New Technique for Study of Cerebral Circulation*

THE BRAIN is unique in that it is supplied with blood by at least four arteries and drained by at least two veins, and is enclosed in a box of hard and soft tissue supplied and drained by the same vessels. These characteristics make the measurement of cerebral blood flow extremely difficult. Techniques applicable to other organs are not suitable for the study of the cerebral circulation. Older methods, such as the nitrous-oxide technique of Kety and Schmidt and its variations, measure cerebral blood flow only through the brain as a whole. In addition, these methods are uncomfortable for the subject and require punctures of arterial vessels and the jugular vein. Certain newly developed techniques for the measurement of regional cerebral blood flow require catheterization of the internal carotid artery, which may be dangerous, particularly to patients with cerebrovascular disease.

The use of the scintillation camera, or "gamma camera," for the study of the cerebral circulation, as reported by Loken and associates, is a new technical approach based on well-known theories. Of the methods these investigators use for distributing a radioactive indicator to the brain, the one in which 133-xenon is inhaled by the subject is of greatest interest, because of the relative comfort to the subject and potential freedom from complications.

In theory, the gamma camera could be used to measure intracranial blood flow in two ways. The appearance and disappearance of an indicator in two locations in an artery, such as the middle cerebral artery, could be recorded and blood flow through the artery determined. Alternatively, the appearance and disappearance of an indicator in an area of brain relatively free of arterial and venous vessels could be recorded, and blood flow through a volume of brain tissue determined. For either type of measurement, the resolution of the detector must be very high, both in space and in time. If Loken and colleagues are able to obtain pictures of isotope distribution in the brain at intervals approaching one second, as they state, resolution in time is approaching adequacy; however, as can be seen in their photographs, resolution in space is far from being adequate for quantitation.

Some question the need for a quantitative measure of cerebral blood flow for clinical practice. Certainly the cerebral circulation can be studied qualitatively very well by angiography. But quantitative measurements of cerebral blood flow are valuable in physiologic

*Loken, M. K., Pierce, Robert, Resch, Joseph, Lassen, Niels, and Ingvar, David: Regional Circulation in the Brain Using a Scintillation (Anger) Camera. Minnesota Med 50:497, 1967.



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studies in humans and animals and may have considerable potential application in studies of drugs and other types of treatment of cerebrovascular disease. Quantitative measurements also may prove to be valuable in diagnosis, such as in differentiating ischemic cerebrovascular disease from hemorrhagic cerebrovascular disease and tumors. And perhaps by safe quantitative techniques the stroke-prone person can be distinguished from others not as likely to develop a cerebral infarct.

Older methods for the study of the cerebral circulation, although valuable for investigations of small numbers of subjects, will not have wide clinical application because of difficulties of technique. Whether or not newer methods, such as those proposed by Loken and co-workers, will be suitable for clinical use will depend upon whether or not these techniques can be developed to provide more information, or enough information more safely, than angiography.

Arthur G. Waltz, M.D.
Rochester, Minnesota

Pointing in the Right Direction

ADHERENTS OF the basic medical sciences have generally ridiculed theories of behavior because they seemed to be without scientific validation. Dr. Buckley's article,* one hopes, is only one of many forthcoming papers laying the foundations of the neurophysiology of behavior. Some day, even the purest of purists will comprehend the correlations between brain and behavior and accept psychology as an important variable in all studies of function and disease. Neurophysiologic ground rules are basic, imperative. Dr. Buckley "points us in the right direction," a direction leading to a better understanding and correlation of scientific data which may set aside for always the dualistic theory of mental function. One can only feel a deep sense of humility in the face of man's ignorance of self—and admiration for his zeal for scientific knowledge to find a better place in the sun.

*Buckley, R. E.: The Brain: Some Psychobiologic Ground Rules for the Lifegame. Minnesota Med 50:1631, 1967.

Richard M. Steinhilber, M.D.
Rochester, Minnesota

Test Your Word Score

Prosthesis—*Greek: an addition* (page 179).

Ristocetin—*an antibiotic useful against staph* (page 187).

Proteolysis—*cleavage of proteins with formation of simpler and soluble products* (page 188).

Nestor—*an old man pre-eminent for wisdom* (page 190).

Vortex—*mass of liquid having a whirling motion tending to form a vacuum in the center* (page 191).

Atopic—*allergic with exudative reaction following exposure* (page 199).

Bleb—*a skin vesicle filled with fluid* (page 211).

Dermatome—*an instrument for incising the skin* (page 213).

Hapten—*an incomplete antigen incapable of producing antibodies but capable of neutralizing specific antibodies* in vitro. (page 290).

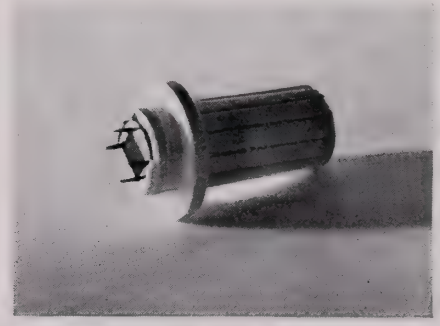


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The Editor's Soliloquy

Anima Sans Sexus

After serving its master faithfully and obediently for years and across two continents: during calm and storm, rain and shine, through sparse or congested traffic, in city, suburb and country, it suddenly rebelled! Heading for the Emergency Ward at the hospital among the hectic permutations and combinations of the crawling, downtown rush-hour exodus, my car horn abdicated—abruptly renouncing all responsibility to remain silent. Scorning timid pianissimo and irresolute staccato, it blared forth sostenuto and fortissimo—with all the authoritative dignity of a Mercedes 250SE Cabriolet. Nor would it cease!

Tapping, pulling, jerking, twisting, banging and kicking at the horn wheel and its contiguous structures were all ridiculously and humiliatingly futile. To add insult to injury, the impudent gremlin within remained relentlessly immune to cajolery and impervious to invectives.

The driver ahead beckoned angrily for me to proceed around and pass him —if I was so all-fired anxious. As I hastened to do so in frantic search of a haven—where I might get relief and be again reduced to the status of anonymity, the oncoming traffic yielded me an ever-widening safety margin for fear of being mowed down—as if a sheer lunatic had been precipitated out of nowhere right into their confounded midst. Faces of bystanders registered a gambit of mixed emotions: from amusement and contempt to defiance, outrage, and even horrified suspicion that I might be harboring an invisible dying emergency or hiding a corpse out of sight on the floor of my car. For certainly I was the only visible occupant in an imposing-looking car that would not be expected to go on a spontaneous rampage—like some of the contraptions wired together by half a dozen teen-age boys.

In spite of—maybe because of—my mortifying predicament, spectators' visages spoke louder than words; my fecund imagination translated their facial expressions into: What's your trouble? Who do you think you are? What's the hurry, man? Think you own the whole street, wise guy? Where's the fire?

Was I perchance rehearsing for a Keystone Comedy film sequence, they must have wondered. Or might I be pursuing a marauding bandit or an eloping daughter? Or had I maybe lost my place in a blithe wedding procession —or a solemn funeral cortege?

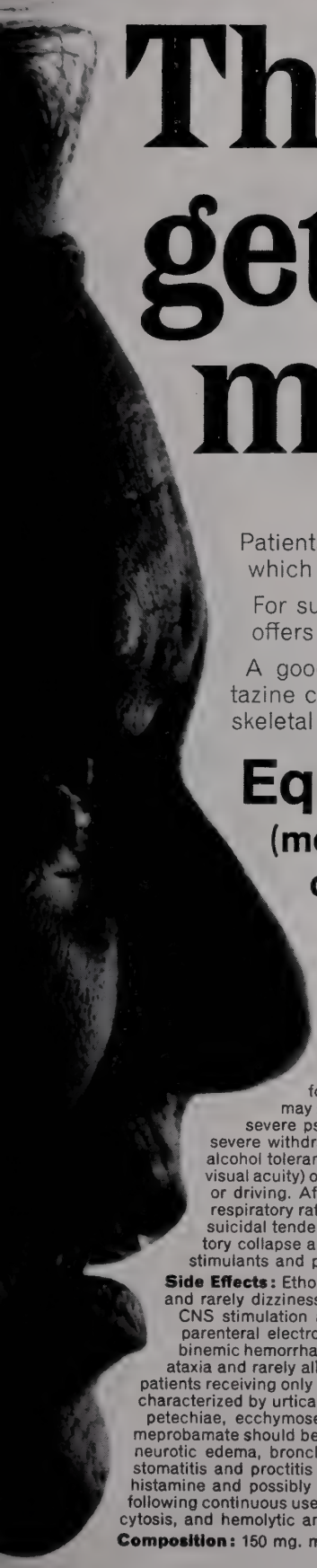
I know of nothing better to humble a man's spirit and relegate him to his proper niche in the cosmic scheme of things than a horn in revolt!

Carl O. Rice, M.D.

Old Doc Hess says: We desire the tranquility of sleep and sweet dreams. Why should we fear the eternal sleep?—C.O.R.

Laugh and the world laughs with you; think and you will almost die from lonesomeness.—Christian Action





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Patients in pain often experience concomitant anxiety and tension, which may add to the burden of pain.

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Contraindications: History of sensitivity or severe intolerance to aspirin or meprobamate.

Warnings: USE IN PREGNANCY: Safety for use during pregnancy or lactation has not been established; therefore it should be used in pregnant patients or women of child-bearing age only when the physician judges its use essential to the patient's welfare.

Precautions: Keep out of reach of children. Not recommended for patients 12 years old or less. Carefully supervise dose and amounts prescribed, especially for patients prone to overdose themselves. Excessive prolonged use of meprobamate may result in dependence or habituation in susceptible persons—as alcoholics, ex-addicts, severe psychoneurotics. Withdraw gradually after prolonged high dosage to avoid possibly severe withdrawal reactions including epileptiform seizures. Warn patients of possible reduced alcohol tolerance. If drowsiness, ataxia or visual disturbances (impairment of accommodation and visual acuity) occur, reduce dose. If symptoms persist, caution patients against operating machinery or driving. After meprobamate overdose, prompt sleep, reduction of blood pressure, pulse and respiratory rates to basal levels, and hyperventilation are reported. Give cautiously to patients with suicidal tendencies. Treat attempted suicide (has resulted in coma, shock, vasomotor and respiratory collapse and anuria) with immediate gastric lavage and appropriate supportive therapy (CNS stimulants and pressor amines as indicated).

Side Effects: Ethoheptazine and aspirin may occasionally cause nausea, vomiting, epigastric distress, and rarely dizziness. Overdosage may result in CNS depression (drowsiness and lightheadedness) or CNS stimulation and salicylate intoxication (requires induced vomiting or gastric lavage, specific parenteral electrolyte therapy for ketoacidosis and dehydration, and observation for hypoprothrombinemic hemorrhage [usually requires whole blood transfusions]). Meprobamate may cause drowsiness, ataxia and rarely allergic or idiosyncratic reactions. These reactions, sometimes severe, can develop in patients receiving only 1 to 4 doses who have had no previous contact with meprobamate. Mild reactions are characterized by urticarial or erythematous maculopapular rash. Acute nonthrombocytopenic purpura with petechiae, ecchymoses, peripheral edema and fever have been reported. If allergic reaction occurs, meprobamate should be stopped and not reinstituted. Severe reactions, observed very rarely, include angioneurotic edema, bronchial spasms, fever, fainting spells, hypotensive crises (1 fatal case), anaphylaxis, stomatitis and proctitis (1 case) and hyperthermia. Treat symptomatically such as with epinephrine, antihistamine and possibly hydrocortisone. A few cases of leucopenia, usually transient, have been reported following continuous use. Rarely, cases of aplastic anemia (1 fatal case), thrombocytopenic purpura, agranulocytosis, and hemolytic anemia have been reported; almost always, in the presence of known toxic agents.

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Curbstone Consultation

Hip Disability

QUESTION: Disability rating continues to pose problems for the medical profession and, accordingly, certain pertinent questions can be raised under the heading of "hip disability." What is an equitable disability rating for a male patient with loss of the leg at the level of amputation with a normal hip joint? What rating for a man with an artificial hip joint?

ANSWER: The following case, summarized from time of injury through Industrial Commission settlement, may help in the evaluation of similar cases as well as of various other hip conditions requiring disability rating.

A 49-year-old mechanic fell on August 30, 1963, and injured his right hip. Though it was painful, he continued working for two days before seeing a doctor. An x-ray study of the hip was read as negative. Although he was never free of symptoms, he continued to work. In the fall of 1964, his pain became increasingly severe and was accompanied by snapping of the hip on motion. X-ray studies then revealed an avascular necrosis with collapse of the femoral head. He was hospitalized for a period of skeletal traction, then operated upon, and a femoral head prosthesis was inserted.

The outcome, a year later, would be considered the usual result of such a salvage operation. He walked with a cane and had slight pain and some generalized muscle atrophy. There was full extension and 105 degrees of flexion, 10 degrees external and 10 degrees internal rotation with about one-half the normal range of abduction present. The involved extremity was one-half inch shorter than its normal length.

The permanent partial disability rating arrived at in an Industrial Commission hearing was 40 per cent of the lower extremity. By comparison, an arthrodesis of the hip in optimum position would receive a rating of 50 per cent. A hip fracture treated by open reduction and followed by good healing with an average end result would be rated at 15 per cent disability. In instances where shortening occurs, 5 per cent disability is usually considered to be a fair rating for each half inch of shortening.

David J. Nelson, M.D.
Minneapolis, Minnesota

Predatory Human Hands

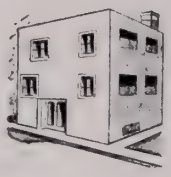
The sun and the moon and the stars would have disappeared long ago . . . had they happened to be within the reach of predatory human hands.—Havelock Ellis

---

Being unable to make what is just strong, we have made what is strong just—Pascal

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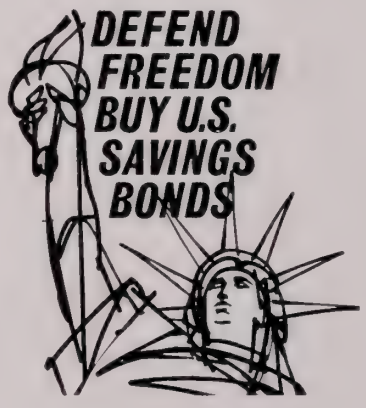
For displasia of the hip in the newborn and in early postnatal life as described by Dr. V. L. Hart, Journal of Bone and Joint Surgery, Vol. 31-A, pp. 357-372, April 1949)

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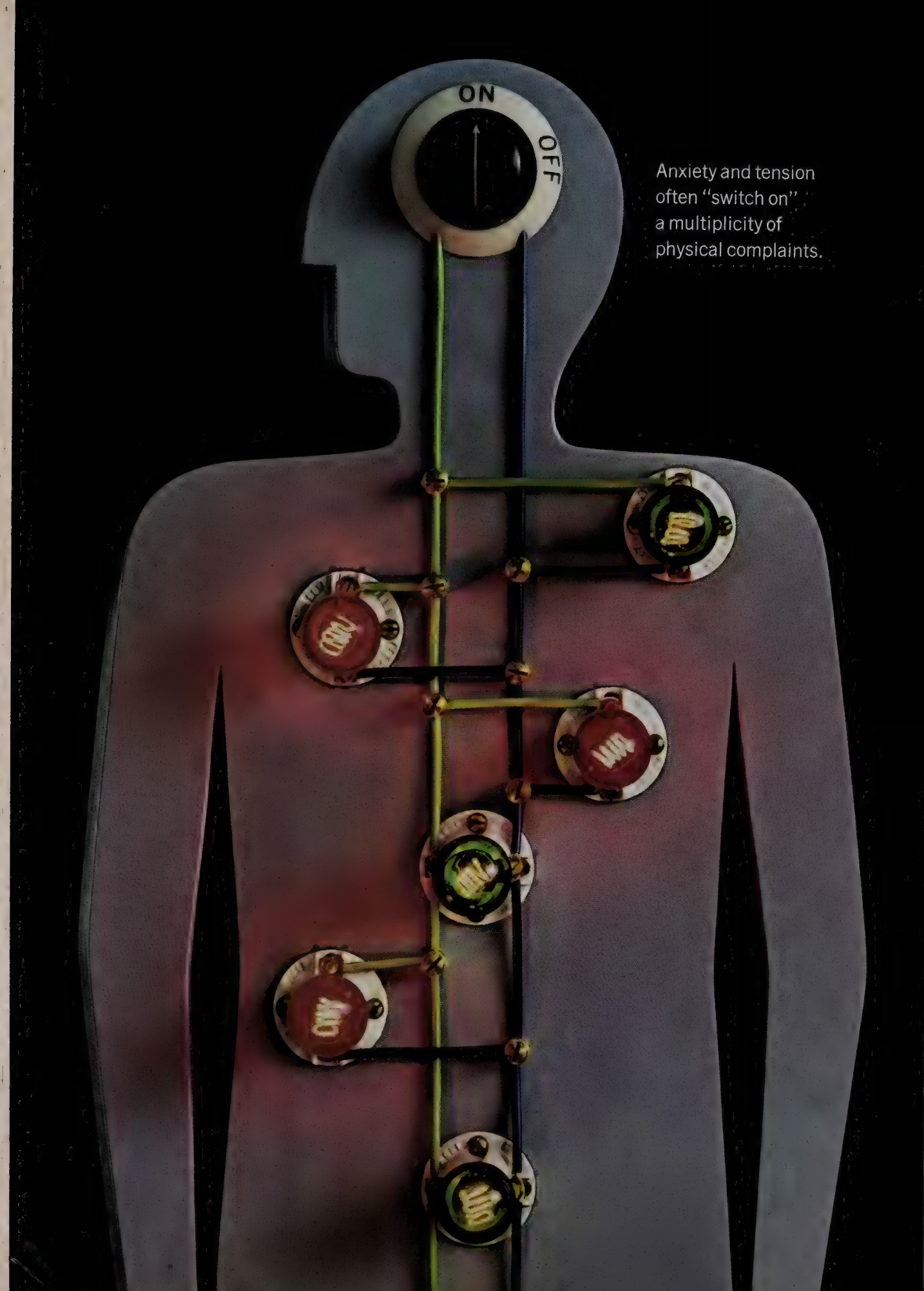
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Contraindications: Hypersensitivity to antihistamines. Not recommended for use during pregnancy.
Precautions: Until patient's response has been determined, he should be cautioned against engaging in operations requiring alertness. Administer with care to patients with cardiac or peripheral vascular diseases or hypertension.
Side Effects: Hypersensitivity reactions including skin rashes, urticaria, hypotension and thrombocytopenia, have been reported on rare occasions. Drowsiness, lassitude, nausea, giddiness, dryness of the mouth, mydriasis, increased irritability or excitement may be encountered.
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Two salient features seem to set Tybatran somewhat apart from certain other commonly used tranquilizers.

1. Tybatran often proves more effective than meprobamate and chlordiazepoxide. In one study,[4] severe anxiety responded more effectively to tybamate than to meprobamate; in another,[8] symptom-response superiority of tybamate over chlordiazepoxide was marked at statistically significant levels of confidence.

2. Tybatran appears to be less sedating than other widely used tranquilizers. Side reactions are relatively infrequent; when they do occur, they may take the form of drowsiness, although insomnia, ataxia and other adverse effects have been reported. Nevertheless, Tybatran impresses many clinicians by its comparative lack of undesirable sedative action.[3,6,12,13] (If drowsiness or vertigo is present, activities requiring optimal alertness should be avoided.)

For patients in whom anxiety is manifested in any of a multiplicity of physical complaints, Tybatran deserves a clinical trial. These are the challenging patients, those with recurrent, persistent, ever-changing symptoms for which there is no clinical or laboratory evidence of organic disease.

Usual adult dose: one or two 250 mg. capsules 3 or 4 times daily. Adjust to suit individual requirements.

A·H·ROBINS

Prescribing Information

Dosage and administration. The suggested adult dose of Tybatran (tybamate) is one or two 250 mg. capsules three or four times daily. Dosage should be adjusted to suit individual requirements. While clinical experience with Tybatran (tybamate) in children has been very limited to date, the recommended daily dosage for children 6 to 12 years old is 20 to 35 mg./kg. body weight, in three or four equally divided doses. Dosage should be adjusted to suit individual requirements. Until further clinical experience is obtained, administration of Tybatran (tybamate) to children under 6 years of age is not recommended. Daily doses larger than 3000 mg. are not recommended, although in a few instances doses in excess of this figure have been administered. Tybatran (tybamate) is also available in 350 mg. capsules, for convenience in dosage adjustment, e.g., one capsule three times daily and two at bedtime.

Contraindications. Tybatran (tybamate) should not be administered to patients known to be hypersensitive to the drug. Since no studies have been done with this drug in human pregnancy, it should not be used in pregnancy unless the potential benefit outweighs the risk.

Warnings. Simultaneous administration to psychotic patients of tybamate with phenothiazines and other central nervous system depressants has in a few instances been associated with the occurrence of grand mal or petit mal seizures. Seizures have been reported with administration of phenothiazines alone, but not with administration of tybamate alone; nevertheless, tybamate should be used cautiously in individuals who are receiving other central nervous system depressants or have a history of convulsive seizures. Also, it should be borne in mind that simultaneous administration of tybamate with alcohol or with other psychotropic agents, particularly phenothiazines or monoamine oxidase inhibitors, which are known to potentiate the action of other drugs, may result in additive actions.

Precautions. There has been no evidence to date of the development of habituation or addiction. Investigators have not observed excessive self-medication or any withdrawal symptoms with use of Tybatran (tybamate), but the latter should be kept in mind with cessation of the drug after prolonged use. Because of the occurrence of

Prescribing information continued on next page.

(pronounced TYE-buh-tran)

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a tranquilizer with particular usefulness in functional disorders

Prescribing information continued from preceding page.

withdrawal symptoms or exacerbation of presenting symptoms upon rapid withdrawal of other agents of this type, abrupt withdrawal of Tybatran (tybamate) should be avoided. Tybamate, like other psychotherapeutic agents, should be used with caution in addiction-prone individuals. Should symptoms of hypersensitivity occur, administration should be discontinued at once and appropriate symptomatic treatment initiated. Operation of motor vehicles or machinery or other activities requiring optimal mental alertness should be avoided if drowsiness or vertigo is present. As with any new drug, Tybatran (tybamate), should be used with caution in patients with a history of drug allergies, blood dyscrasias, and hepatic or renal disease; and prolonged and/or high doses of tybamate should be accompanied by periodic measurements of hepatic, hematopoietic, and renal function.

Adverse reactions. While these have only rarely required discontinuation of the drug, the most frequently encountered reactions have included drowsiness, dizziness, nausea, insomnia, euphoria. The drug was discontinued in one child because of a possible drug-induced urticaria, and skin rash and pruritus have been encountered in a few other patients. In a few patients, effects suggesting excessive stimulation such as hyperactivity, fidgetiness, flushing, and tachycardia have been encountered. Other reported side effects recorded only a few times to date have included ataxia, unsteadiness, confusion, feeling of unreality, "panic reaction," fatigue, headache, paresthesias, vertigo, gastrointestinal disturbances, glossitis and dry mouth. Grand mal or petit mal seizures have been reported in a few hospitalized psychotic patients to whom tybamate (up to 6000 mg. daily), phenothiazines, and other psychotropic agents were administered simultaneously. Convulsive seizures have not been reported with the use of tybamate alone.

Until clinical experience has accumulated with this drug, inasmuch as tybamate is related to meprobamate, the physician should be cautious about the possibility of rare, serious adverse reactions such as may be encountered with the latter drug. Should excessive doses of tybamate be ingested, it is recommended that any drug remaining in the stomach be removed and symptomatic therapy, including central stimulants, be used as necessary.

Supply. Tybatran (tybamate) is available in green, sealed capsules of three strengths: 350 mg., 250 mg., and 125 mg. Each strength is supplied in bottles of 100 and 500.

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Juvenile Diabetic

THE RETROGRADE pyelogram pictured below is that of a 35-year-old female juvenile diabetic. Over the past 20 years she has been hospitalized nine times for recurrent pyelonephritis. E. coli, Proteus, and Aerobacter have on different occasions been cultured from her urine.

For three days prior to the current admission she had experienced left flank pain of a colicky nature radiating into the groin and accompanied by vomiting, fever, and dysuria.

On admission her temperature was 102°, B.P. 108/60, pulse 124, and respirations 24. Urinalysis revealed 3+ glucosuria, acetone positive, with 125 wbc. and 35 RBC/hpf. Her BUN was 21 mg%, blood sugar 293 mg%, and CO_2 17.5 meq/1.

The retrograde study antedates the current admission by several months. The right kidney is relatively normal. You will notice that the normal cup-shaped appearance of the minor calyces on the left is compromised. The smooth outline of the calyceal fornices is, however, preserved and the renal pelvis and the proximal ureter appear normal.

What is your diagnosis? (See next page.)



Fig. 1—Flask-shaped defects are demonstrated (arrows) within the papilla.

Diagnosis: Renal Papillary Necrosis

The basic pathology of renal papillary necrosis involves ischemic infarction of the renal papilla. The renal papilla is particularly susceptible to vascular compromise because of its blood supply consisting of: (1) vessels from the glomeruli which seldom anastomose and (2) small spiral arteries from the adventitia of the minor calyces that penetrate the papilla. Compression of these vessels from pressure or edema may result in necrosis.

Etiologic factors include:

1. diabetes mellitus
2. chronic pyelonephritis
3. phenacetin abuse
4. urinary tract obstruction
5. sickle cell disease or trait
6. renal vein thrombosis
7. shock

Radiologic examination is the only reliable method of diagnosis of renal papillary necrosis during life unless papillary fragments are passed or the kidney is biopsied or excised.

Many of the early radiographic findings in renal papillary necrosis are nonspecific; local reduction of function, irregular papilla, and dilatation of fornices. These changes may be seen in common pyelonephritis and in renal tuberculosis.

The classification of renal papillary necrosis used today was recorded in 1948 by Gunther, who divided it into two types: the medullary and papillary forms based on the extent of necrosis. The tip of the papilla only is destroyed in the medullary type with preservation of the calyceal fornix. In the papillary type the entire papilla is involved including the fornix and varying portions of the renal pyramid. In either type the papilla is sequestered, producing on urographic study the characteristic "ring sign." Contrast surrounding the less dense necrotic papilla within the calyx creates this "ring sign." Later in the course of renal papillary necrosis the necrotic papilla is sloughed away or resorbed, leaving a flask-shaped defect in the papilla, as in the presented case, or a "clubbed" calyx. If the necrotic papilla remains in the calyx, it will usually calcify and appear on radiographic examination as a concretion with a radiolucent nidus.

In 1877 von Friedreich first described renal papillary necrosis in an elderly man with prostatic hypertrophy and chronic urinary tract obstruction. He ascribed the necrosis to kinking of the papillary vessels interfering with the blood supply, and he implied that flattening of the papillary regions in hydronephrosis could in certain cases be due to papillary necrosis, and that the papillary fragments voided might allow antemortem diagnosis.

As late as the mid-1950s renal papillary necrosis was generally regarded as a complication of diabetes mellitus or chronic urinary tract obstruction frequently associated with infection. It was held to be a highly fatal disease. The glomerulosclerosis and arteriosclerosis of the diabetic Kimmelstiel-Wilson kidney or the elevated intrapelvic pressure of obstruction combined with infection infarct the papilla. The outstanding clinical characteristic of this fatal type of renal papillary necrosis is a sudden marked worsening of the patient's general condition, with colic, hematuria, fever, and uremia.

In recent years a new type of renal papillary necrosis has emerged with a better prognosis. Chronic phenacetin ingestion is the cause. In the two

largest series of renal papillary necrosis thus far reported, totaling 258 cases, the predominant etiologic factor was phenacetin abuse. A minimum of one gram daily for at least one year or a cumulative dose of approximately one kilogram is felt to be necessary before the nephrotoxic effect of phenacetin results in interstitial nephritis and renal papillary necrosis.

Phenacetin is found in many of the commonly used and perhaps abused proprietary analgesics: Anacin, Anahist, APC tablets, aspirin compound, Bromo-quinine decongestant, Coricidin, Empirin compound, and Vick's cold tablets.

A very frequent association of migraine-like headaches and abuse of phenacetin is reported by the Scandinavian authors.

The caffeine, codeine, and barbiturates compounded with phenacetin contribute to the problem of addiction. Phenacetin-induced renal papillary necrosis is usually chronic and may be partially reversible after withdrawal of the medication. For this reason a history of phenacetin abuse can be an important although often occult bit of information.

Sickle cell disease and trait are also known to cause renal papillary necrosis. Conditions in the renal papilla are ideal for sickling. The oxygen tension within the kidney is known to diminish from the cortex to the papilla, and the interstitial fluid of the papilla is of high osmolarity. Papillary infarction is the end result of this type of vascular insult.

Renal papillary necrosis is most often a disease of middle age but is seen in infants and the aged. It may be acute or chronic. It is usually bilateral, but may be unilateral. Seven females are affected for every male. The prognosis depends on the primary cause and complications and the efficacy with which these are treated.

H. James Ver Steeg, M.D.*
Minneapolis, Minnesota

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It is easier to understand a nation by listening to its music than by learning its language.—Anonymous

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A brain weight of nine hundred grams is adequate as an optimum for human behavior. Anything more is employed in the commission of misdeeds.—Earnest Hooton

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The artist doesn't see things as they are, but as he is.—Anonymous

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In every work of genius we recognize our own rejected thoughts; they come back to us with a certain alienated majesty.—Emerson



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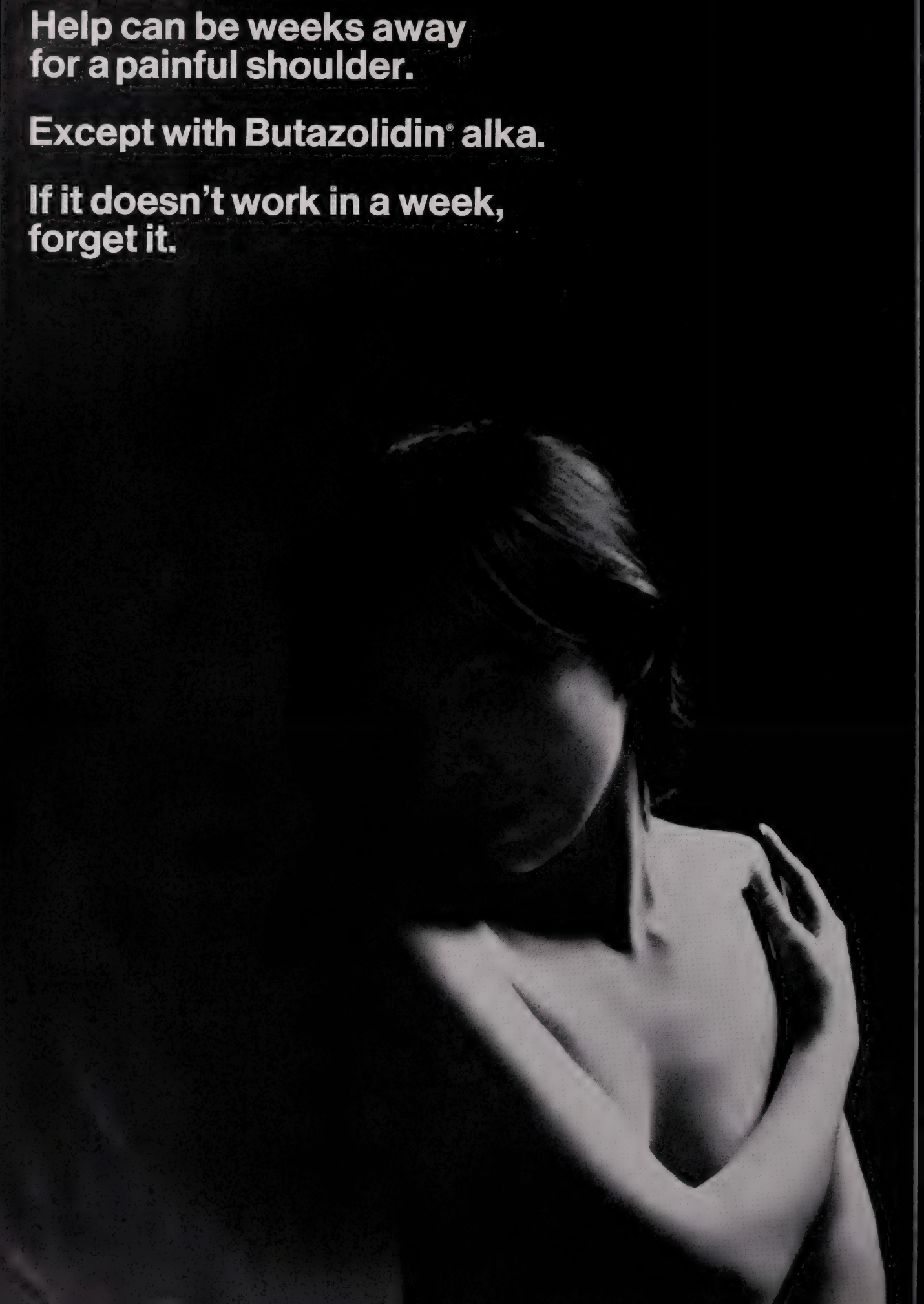
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Precautions: Before prescribing, carefully select patients, avoiding those responsive to routine measures as well as contraindicated patients. Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patient should not exceed recommended dosage, should be closely supervised and should be warned to discontinue the drug and report immediately if fever, sore throat, or mouth lesions (symptoms of blood dyscrasia); sudden weight gain (water retention); skin reactions; black or tarry stools or other evidence of intestinal hemorrhage occur. Make regular blood counts. Discontinue the drug immediately and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.

Adverse Reactions: The most common are nausea, edema and drug rash. Swelling of the ankles or face may be minimized by withholding dietary salt, reduction in dosage or use of diuretics. In elderly patients and in those with hypertension the drug should be discontinued with the appearance of edema. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. The patient should be instructed to take doses immediately before or after meals or with milk to minimize gastric upset. Mild drug rashes frequently subside with reduction of dosage. However, rash accompanied by fever or other systemic reactions usually requires withholding medication. Purpuric rash has also been reported. Agranulocytosis, exfoliative dermatitis, Stevens-Johnson syndrome, or a generalized allergic reaction similar to serum sickness may occur and require permanent withdrawal of medication. Stomatitis, salivary gland enlargement, vomiting, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported. While not definitely attributable to the drug, a causal relationship cannot be excluded. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.



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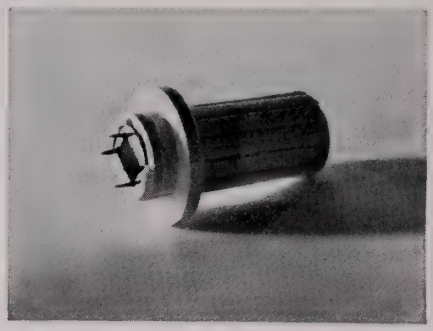
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Trauma Conference

Osteochondral Fractures of the Talus

(Osteochondritis Dissecans)

OSTEOCHONDRAL FRACTURE of the talus is not a common disease entity. No large series of cases has been recorded. This may account for the lack of consensus regarding therapy. Berndt and Harty in 1959 presented an excellent review of the literature with a detailed analysis of cases including experimental studies and arrived at two conclusions. First, that trauma is almost always the etiologic agent. Second, that surgical removal of the fragment gives the highest percentage of good results in symptomatic patients.

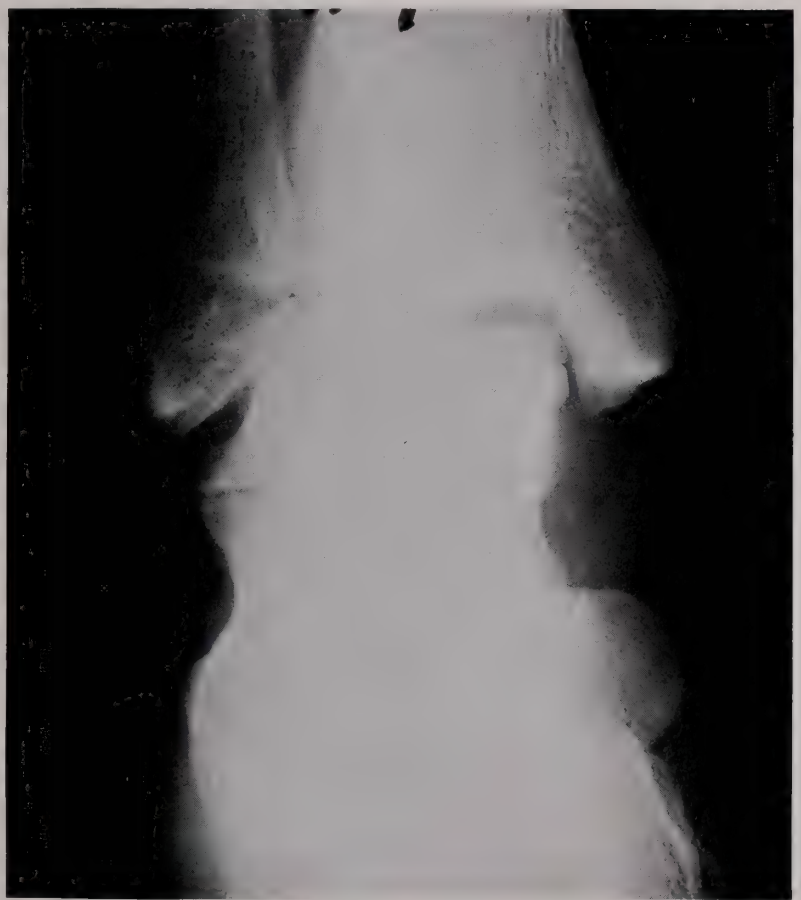


Fig. 1—AP ankle. Note radiolucent line surrounding detached fragment along the superior articular surface of the talus medially.

They also pointed out that the majority of these patients are asymptomatic.

This study is an analysis of ten cases of osteochondral fracture of the talus seen at the St. Louis Park Medical Center, Minneapolis, Minnesota, from 1953 to 1965. Six out of 10 patients gave a definite history of trauma. Four patients came in because of chronic recurrent pain, aching, and swelling of the ankle with no antecedent history of injury. The age range was from seven to 72 years. On x-rays of the ankle, seven out of 10 showed a defect in the lateral aspect of the talus superiorly. The duration of signs and symptoms ranged from one to 63 years. Followup was made in nine patients varying from one to 12 years. These patients were treated conservatively in various ways from a short-leg walking cast to crutches, Ace bandages, rest, elevation, and no treatment at all.

The typical x-ray finding is one of a zone of radiolucency or a depressed fragment either medially or laterally on the superior articular surface. Sometimes a clear zone of radiolucency is seen around a sclerotic fragment. A secondary degenerative arthritis can be found either at the medial or lateral side of the ankle joint in cases where there is a long history of signs and symptoms. Soft tissue swelling around the ankle is seen in cases where acute trauma preceded the onset of symptoms.

The detailed analysis of every patient seen at the St. Louis Park Medical Center is outlined in Table 1.



Fig. 2—Oblique ankle. Better demonstration of detached but undisplaced fragment.

Case Reports

Case 1:

This 13-year-old girl was seen at the St. Louis Park Medical Center in 1956 because of occasional pain, swelling, and restricted motion of the ankle. The patient denied any history of trauma at any time in the past. Pertinent orthopedic findings on physical examination were limited to slight swelling with minimal discomfort on extreme range of motion. X-rays taken October 27, 1956, showed a typical radiolucent zone on the medial aspect of the talus, and

TABLE I
Osteochrondritis Dissecans (Osteochondral Fracture of the Talus)
Summary of Results

Patient	Patients' Age	S & S	Treatment	Followup	Results
1. P.A.	13 years	Occasional pain, swelling, & restricted motion. No history of trauma.	Short leg cast for eight weeks.	Ten years	Asymptomatic.
2. A.J.	10 years	Pain & swelling aggravated by running, jumping, etc. Twisted left ankle.	Rest, crutches for two weeks.	One and one-half years	Still has pain & recurrent swelling on heavy activities.
3. E.F.	63 years	Recurrent aching & swelling of ankle of several years duration. No history of trauma.	Rest, Colchicine & Benemid for his gout appeared to help.	Five years	Asymptomatic.
4. S.T.	26 years	Twisted left ankle, pain & swelling.	Short leg cast, four weeks.	Nine years	Asymptomatic.
5. D.B.	12 years	Twisted left ankle, pain & swelling.	Compression bandage, seven days.	None	Not known.
6. B.C.	72 years	Injured foot & ankle at 9 years of age. Progressive pain & swelling with marked limitation of motion.	None.	Sixty-three years	Pain, swelling, advanced degenerative arthritis of ankle joint.
7. M.S.	62 years	Twisted left ankle. Pain & swelling, fracture lateral maleolus. Osteochondral fracture, medial talus.	Short leg cast for six weeks.	Two years	Occasional pain & swelling.
8. E.K.	26 years	No history of trauma. Pain lateral ankle area. Minimal swelling.	Heat, ankle support, aspirin.	One and one-half years	Asymptomatic.
9. M.L.	9 years	Fall from a merry-go-round. Pain & swelling. Undisplaced fracture of fibula also.	Cast for ten weeks.	Six years	Fracture healed. Occasional pain & swelling aggravated by excessive use of foot and ankle.
10. H.R.	36 years	Injured ankle playing baseball in grade school. Chronic aching & giving way of ankle when involved in running, baseball, etc.	None.	Five years	Symptomatic only when running up stairs & sliding. Occasionally aches. X-ray early arthritis medial side of ankle joint.

a diagnosis of osteochondritis dissecans was made (Figure 1). The patient was treated for eight weeks in a short leg cast. Followup x-ray studies in 1960 and 1965 again showed the detached but undisplaced fragment on the medial side of the talus in almost identical position. The osteochondral fracture had not united in ten years. In 1960 the patient was only slightly symptomatic when involved in very vigorous activities like running and jumping. Ten years after the initial x-ray the patient is completely asymptomatic.

Case 2:

A 27-year-old white male sustained an Achilles tendon rupture May 28, 1965, while playing baseball. X-rays taken of the ankle showed an osteochrondral fracture at the medial end of the talus (Figure 2.) The patient states that for several years he had aching pain and a "giving-out-sensation" in the ankle following a football or baseball game. He denies any history of trauma just before onset of symptoms.

A primary repair of the Achilles tendon was done.

The right leg was placed in a long leg cast for six weeks and a short leg cast for four weeks.

On last examination, July 21, 1956, the osteochondral fracture appears unchanged. The patient is now asymptomatic even on prolonged standing or running. The ruptured Achilles tendon has healed without complication.



Fig. 3—(Case 2) (left) radiolucent defect appears to lie below the articular surface. (Right) radiolucent defect involves medial superior corner of articular surface. Small bone fragment is seen within the radiolucent zone.

From this study it appears that only two patients out of ten were definitely symptomatic. In these two patients the symptoms were probably due to secondary degenerative arthritis. Three patients were symptomatic only on excessive use of the foot or ankle, as in running, prolonged walking, or jumping. The other patients were completely asymptomatic. From this small number of cases, it would appear that many of these patients do not have symptoms. It would indicate, however, that if the patient is symptomatic, a more vigorous approach to the problem is needed. This is preferred to merely observing the patient in order to prevent development of a secondary degenerative arthritis. It is recommended that these patients be placed in a cast for three months, allowing sufficient time for the osteochondral fracture to unite, especially when a history of trauma is given. If, after three

months, the patients continue to have symptoms, the removal of the fragment is indicated as recommended by Berndt and Harty in their series.

Ramon B. Gustilo, M.D.*
Sewell S. Gordon, M.D.*
Minneapolis, Minnesota

*St. Louis Park Medical Center. Reprints may be secured from the St. Louis Park Medical Center, 4959 Excelsior Boulevard.

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Audio-Analgesia

Music to ease pain has been used for some time without any great scientific concentration on its possibilities. Today, a greater amount of attention is being focused on this particular area. Experiments are currently under way in which music and special static sound effects, known as "white sound," are played to a patient during certain types of dental or minor surgery. Preliminary results indicate that these combinations of relaxing music and somewhat disturbing white sound crowd the thalamus and cerebral cortex with a high level of sensory input and seem to reduce the sensation and recognition of pain.*

*Bernard Seeman: Man Against Pain.

Into the Hold

The police played a tremendously important part in my life as an ambulance surgeon. I discovered when I started duty that not only could I count on the faithful drivers to lift and carry for me, but that, the minute I mounted the tailboard, I acquired the rank of Sergeant of Police, and could command as many roundsmen as I needed. I remember on one occasion finding myself on a rope ladder—probably a policeman just below me, and another one just above. It had not occurred to me that I might fall off, and I was wondering why it was necessary to have those two policemen, and whether the ladder could possibly hold all three of us. Undoubtedly they decided when they saw me arrive with the ambulance that they would not take the chance of my falling off on that hazardous little trip down into the bowels of the ship. In this case had I hesitated and looked down into the dizzy depths of the hold, I might easily have become panic-stricken. And so in solemn though vertical procession, we three reached the bottom safely, where I found that a sailor had fallen into the hold. He had landed on his feet, fracturing some of the small bones. I put his feet into splints and prepared him as carefully as I could for his removal to the hospital, and we retraced our steps up the swinging ladder, a policeman above me and one below, "just in case."*

*Emily Barringer, M.D.: Memoirs of a Lady Ambulance Surgeon, Bowery to Bellevue, 1950.

Most people eat as though they were fattening themselves for the market.—E. W. Howe

Originality does not consist in saying what no one has ever said before, but in saying exactly what you think yourself.—Stephen

The oldest books are still only just out to those who have not read them.—Samuel Butler

Sometimes, Madge will surprise you.



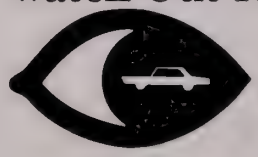
Surprise!

Madge has her mind set on a new set of drapes. And it could mean "curtains" for you. It's surprising how many people are surprised like that every year.

Don't be.

Wherever, whenever you drive . . . drive defensively. Watch out for the other guy, or gal.

Watch Out for the Other Guy.



Published to save lives in cooperation with The Advertising Council and the National Safety Council.

Sources of sinus headache



REGION OF SENSATION

FRONTAL SINUS—headache localized over the frontal region, commonly beginning in the morning. Eyes painful to touch, may be slight swelling over eyes, puffy eyelids.

SPHENOID SINUS—most difficult to diagnose. Headache or sense of pressure over vertex. May be pain in ear or mastoid region.



MAXILLARY SINUS—headache and tenderness under eyes at top of cheekbones, usually starting in early afternoon. Possible swelling of cheek. Pain in jaw and back teeth.

ETHMOID SINUS—headache, tightness in upper part of bridge of nose and well down its sides. Pain, deep-seated behind the eyes and in inner corners of the eyes.



TURBINATES—pain along medial and lateral walls of the inside of the nose. Headache in frontal region, along supraorbital ridge, a feeling of fullness in the head.

Source of symptomatic relief

SINUTAB



Sinus headache is often a reflection of congestion in the nasal mucosa. The pain that results in the various regions of the head may help in determining the particular structure(s) responsible. The Sinutab formula is specifically designed for symptomatic relief of sinus headache and nasal congestion. **Sinutab** *not only* **provides an effective decongestant** — to reduce mucosal engorgement and facilitate freer breathing — *and* **an antihistamine** — to help reduce edema and excessive secretions — but it *also* provides, in contrast to other leading decongestants, **two analgesics** for immediate relief of pain and discomfort.

And, too, the Sinutab dosage schedule of 2 tablets, *q. 4 h.* permits controlled and continuing analgesic relief.

Adverse Reactions: Epigastric distress, drowsiness, dizziness, insomnia and nervousness.

Precautions: Instruct patients not to drive or operate machinery if drowsiness occurs. Use with caution in patients with thyroid disease, heart disease, hypertension, diabetes or kidney disease. Excessive dosage or prolonged use may cause kidney damage.

Dosage: Adults—2 tablets every 4 hours.

Each tablet contains 150 mg. acetaminophen, 150 mg. phenacetin, 25 mg. phenylpropanolamine HCl, and 22 mg. phenyltoloxamine citrate.

SPECIFIC FORMULA **SINUTAB®** FOR SINUS HEADACHE

Also Available on Prescription:

Sinutab® with Codeine.* Each tablet contains 15 mg. (¼ gr.) codeine phosphate (Warning: May be habit forming), 150 mg. acetaminophen, 150 mg. phenacetin, 25 mg. phenylpropanolamine HCl, and 22 mg. phenyltoloxamine citrate.

Sinutab® Pediatric Suspension. Each 5 ml. teaspoonful contains 300 mg. acetaminophen, 12.5 mg. phenylpropanolamine HCl, and 10 mg. phenyltoloxamine citrate.

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S-IN-81-4C

WC **WARNER-CHILCOTT** Morris Plains, N.J.



Tumor Conference

Thymoma?

TUMORS OF THE thymus catch more than average interest since the role of the thymus immunology is just recently coming to light. Even more interesting is the association of thymic tumors with myasthenia gravis. This case illustrates a third frequent source of interest—a tumor, arising in the area of the thymus, which has no other source of origin, but is not a thymoma in the strict sense. The following case also illustrates some of the more sinister elements of thymic tumors. Thymic tumors start in the anterior mediastinum and with continued invasive growth encroach on neighboring structures, causing pain, dyspnea, or signs of superior vena cava obstruction. Nonresectable malignant thymomas may remain asymptomatic for a long time,[1] not being suspected until a chest film shows a mass in the anterior upper mediastinum.

Case Report

A 23-year-old quadriplegic was transferred to the Minneapolis Veterans Hospital on 11/23/65 for evaluation of a right upper chest mass, possibly a traumatic aneurysm of the aortic arch.

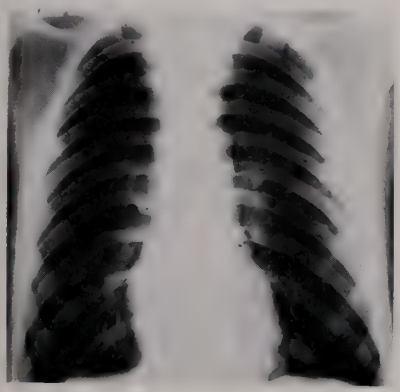


Fig. 1—A chest x-ray taken about one year prior to admission. There were several old granulomata present. The slight widening of the upper mediastinum was not appreciated at that time.



Fig. 2—A chest x-ray taken just before admission showing the huge mass in the right side of the chest.

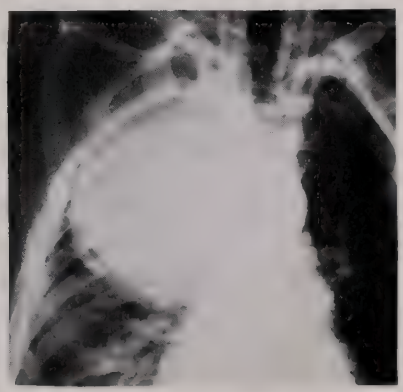


Fig. 3—An arteriogram showing the mass adjacent to, but not involving the aortic arch.

History

The patient had been well before his enlistment in the Army. In 1960, while running an obstacle course, he fractured and dislocated the cervical spine, resulting in quadriplegia. Since 1960 the patient had been treated as an out-patient for upper respiratory and urinary tract infections. Periodic chest x-rays were negative up to one year before admission (Figure 1). However, on a routine posterior-anterior chest x-ray in October, 1965, a mass was noted in the area of the right upper lobe. The patient was asymptomatic. A repeat x-ray in November, 1965, showed a marked increase in the size of the lesion (Figure 2). The patient then began complaining of dyspnea and right upper chest pain when sitting.

Physical Examination

This 23-year-old quadriplegic was in no acute distress. A neurological deficit compatible with a spinal cord transection at the T4 level was present. Blood pressure, pulse and temperature were normal. Arm pressures were equal. The chest expanded well. Dullness and diminished breath sounds over the right upper chest were noted. There were no signs of superior caval obstruction.

Chest x-ray, posterior-anterior and lateral, revealed a large mass, contiguous with the mediastinum, occupying the right upper chest. A retrograde arteriogram showed a normal outline of the central arterial tree with some displacement (Figure 3). Tumor vessels were not demonstrated and an esophagram failed to show esophageal displacement.

Operation

On November 29, 1965, a right posterolateral thoracotomy was performed. A large tumor was found, filling the right chest cavity, compressing the right upper lobe, and extending into the anterior mediastinum. There was an associated atelectasis of the right upper lobe. The great vessels could be dissected from the adjacent tumor. The tumor was excised as widely as possible, but central margins were meager.

Progress

Postoperatively, the patient needed artificial respiration for four days, due to a temporary phrenic nerve palsy. At the time of discharge, the right lung had satisfactorily expanded. The patient was asymptomatic, up in a wheel chair as he had been preoperatively. A pathology report revealed undifferentiated sarcoma, most likely arising in the thymus gland.

For the convenience of the patient's family, follow-up was transferred to his hometown Veteran's Hospital. Eight months later, he was admitted there with hemoptysis and x-ray evidence of local recurrence. He was treated with x-ray (2000 r. tumor dose) and methotrexate, which gave almost one year of palliation. He died 20 months postoperatively.

Comment

Nelms and Nicoloff,[2] reviewing mediastinal tumors over 15 years at Minneapolis V. A. Hospital, found 94 tumors, of which 17 were thymic in origin. It is frequently difficult, as in the illustrative case, to be certain that an anterior mediastinal tumor had its origin in the thymus. It is difficult to exclude tumors which arise in the stroma of the gland, such as fibrosarcoma, myxosarcoma, or liposarcoma. There is the controversy over the origin of the cellular elements of thymic parenchyma. The problem is further clouded by primary and secondary neoplasms which commonly involve the lymph nodes of the anterior mediastinum. The anterior mediastinum is a common site for teratomas and for direct extension of primary tumors of the lung. [3,4] Finally, extensive degenerative changes within the tumor may make its identification on a histologic basis difficult or impossible.

Criteria for Diagnosis

Seybold and Claggett[1] have outlined criteria for establishing a tumor of the anterior mediastinum as a thymoma. They emphasize, as does Castleman,[5] that all other sources should be ruled out. In the instance of a large anaplas-

tic, partially necrotic tumor, with distorted anatomic relationships, there can be no real certainty of thymic origin. The usual thymoma is a slow-growing tumor of the thymus, which has arisen from both the epithelial (reticulum) and thymocytic elements of the thymic parenchyma. The relative proportion of these cells varies greatly from tumor to tumor and often from place to place in the same tumor. Typical Hassall's corpuscles are absent in most thymomas.

Morbidity

Thymomas exert their lethal effect by direct extension and invasion. Embolic metastases either by way of blood or lymphatics are rare. These tumors display few histologic features of malignancy such as hyperchromasia, increased nuclear cytoplasmic ratio, and mitotic figures. This is true even of thymomas, which are not resectable because of gross invasion of contiguous structures. Hence, it is frequently the surgeon and not the pathologist who determines whether the tumor is benign or malignant.

Although a lengthy discussion of myasthenia gravis is not warranted by this case, it is interesting to note that there seems to be no definite histologic pattern by which one can distinguish a thymoma in a patient who does or does not have myasthenia gravis. It is also a well accepted fact that the malignancy of thymic tumors has no relationship to the presence or absence of myasthenia gravis.[6] Furthermore, thymoma can occur either before or after the appearance of myasthenia gravis. Of particular and important interest are cases in which myasthenia gravis may develop abruptly during the early postoperative period following the removal of a thymoma. In the illustrative case, the detection of myasthenia gravis in a quadriplegic patient poses real problems.

The association of thymoma and agammaglobulinemia has been one of the motive observations stimulating interest in the role of the thymus in immune processes.[7] This has been reviewed by Good and co-workers.[8]

Management

Management of these tumors presents problems. Because of their malignant potential (10-25%) and involvement of mediastinal contents all thymic tumors *should be explored and resected,* if at all possible, regardless of whether or not the patient has myasthenia gravis. Every effort to eradicate the tumor surgically must be made, because distant metastases are uncommon and even invasive types may be cured. One may resort to grafting the great vessels in removing the tumor.

The question of the usefulness of *chemotherapy and roentgen therapy* alone and/or combined with surgery has not been well answered. Decker[9] in 1935, in reviewing 206 cases of malignant thymomas, came to the pessimistic conclusion that carcinoma of the thymus will be fatal unless the growth can be successfully removed. He did advocate that roentgen therapy be used in cases of "lymphosarcoma of the thymus."

Brody and Legg [10] reported 10 cases of invasive thymoma. Seven were treated solely by x-ray after biopsy; two had irradiation after attempted extirpation. Four of the ten patients survived five years after therapy and two others were alive at one-and-a-half and two years.

Ochsner and Burch[11] reported 20 thymomas treated in various ways.

Twelve were malignant and eight were benign. A total of 15 patients had only partial excision or biopsy of the tumors. Nine patients were treated with roentgen therapy and six with chemotherapy. Of the nine patients treated by irradiation, seven had malignant tumors and two had benign tumors. Three patients, all with malignant tumors, died. Of the six patients treated with nitrogen mustard, three of the five with malignant tumors are well, and two are dead. The longest survival after roentgen therapy and nitrogen mustard is 14 years in a patient with malignant thymoma. From these studies it seems that x-ray may be a useful adjunct to surgery. Since a significant number of thymic tumors are radiosensitive, particularly those with a large lymphoid component, failure to remove the tumor surgically is not hopeless. Irradiation alone or combined with chemotherapy may be of further definitive or palliative benefit, especially when diagnostic reservations are made as to tumor origin and cell type.

Thomas J. Greene, M.D.*
Donald G. McQuarrie, M.D.*
Minneapolis, Minnesota

*Departments of Surgery, Minneapolis Veterans Administration Hospital and the University of Minnesota.

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The Patient's Role

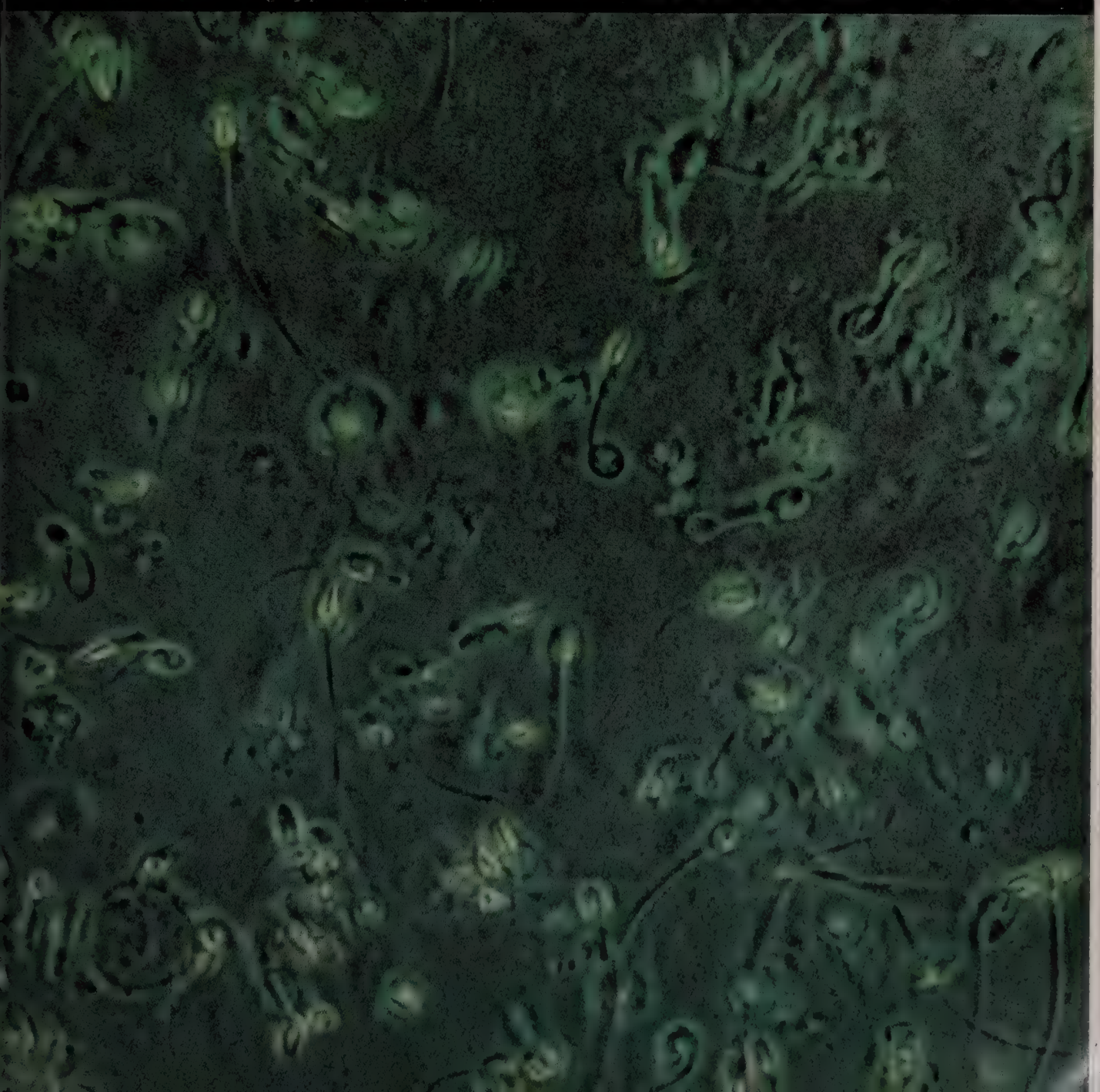
The expression "the patient" sounds as if it meant one definite person, someone who simultaneously is ill and wants help, to whom the doctor is called, and with whom the doctor deals. Usually, however, "the patient" was more than one person (often all of them needing treatment). Sometimes, although the doctor was called by one member of the family for another member who was said to be ill, it might turn out that the caller himself was the sick person, or even that a third person, not mentioned before, was the true patient in need of help. In the majority of cases there was a very complex involvement of all members of the family. The patient for whom the doctor was called might well be ill, but the anxieties aroused in the patient's family were commonly very much in excess of the patient's own anxieties and degree of illness.*

*Max B. Clyne in Richard Magraw: Ferment in Medicine, 1966.

When the talk turns to oral contraceptives, it makes medical sense to remember low-dose Norinyl®-1.

(norethindrone 1mg. c mestranol 0.05mg.)

Turn page for contraindications, precautions and side effects.



Reduction of oral contraceptive dosage to the lowest effective levels is a well-accepted principle of conservative medical practice. In keeping with this view, Norinyl is now also available as Norinyl-1, containing exactly one half the previous dosage of norethindrone and mestranol. Clinical experience has established that effective fertility control can be achieved with the same degree of reliability and safety with new Norinyl-1 when taken as directed.

What about switching patients from higher dosage forms?

In transferring patients to low-dose Norinyl-1 from higher-dosage oral contraceptives, some breakthrough bleeding may occur in the early cycles. In the majority of cases the bleeding episode is mild and self-limited. The long-term advantages of the lower dosage form should be weighed against the inconvenience of possible breakthrough bleeding in the individual patient.

Contraindications: 1. Patients with thrombophlebitis or with a history of thrombophlebitis or pulmonary embolism. 2. Liver dysfunction or disease. 3. Patients with known or suspected carcinoma of the breast or genital organs. 4. Undiagnosed vaginal bleeding.

Warnings: 1. Discontinue medication pending examination if there is sudden partial or complete loss of vision or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn. 2. Since the safety of NORINYL-1 (norethindrone 1 mg. with mestranol 0.05 mg.) in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. 3. Detectable amounts of the active ingredients in oral contraceptives have been identified in the milk of mothers receiving these drugs. The significance of this dose to the infant has not been determined.

Precautions: 1. The pretreatment physical examination should include special reference to breast and pelvic organs, as well as a Papanicolaou smear. 2. Endocrine and possibly liver function tests may be affected by treatment with NORINYL-1. Therefore, if such tests are abnormal in a patient taking NORINYL-1 it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, preexisting uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions that may be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. NORINYL-1 should be used with caution in patients with a history of cerebrovascular accident. 6. In relation to breakthrough bleeding, and as in all cases of irregular bleeding *per vaginam*, nonfunctional causes should be borne in mind. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated. 7. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 8. Any possible influence of prolonged NORINYL-1 therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. 9. A decrease in glucose tolerance has been observed in a small percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving NORINYL-1 therapy. 10. Because of the occasional occurrence of thrombophlebitis and pulmonary embolism in patients taking oral contraceptives, the physician should be alert to the earliest manifestations of the disease. 11. Because of the effects of estrogens on epiphyseal closure, NORINYL-1 should be used judiciously in young patients in whom bone growth is not complete. 12. The age of the patient constitutes no absolute limiting factor, although treatment with NORINYL-1 may mask the onset of the climacteric. 13. The pathologist should be advised of NORINYL-1 therapy when relevant specimens are submitted.

Side effects observed in patients receiving oral contraceptives: The following adverse reactions have been observed in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea, edema, chloasma or melasma, breast changes (tenderness, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately postpartum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals, mental depression.

Although the following side effects have been reported in users of oral contraceptives, no cause and effect relationship has been established: anovulation post-treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, itching.

The following occurrences have been observed in users of oral contraceptives (a cause and effect relationship has been neither established nor disproved): thrombophlebitis, pulmonary embolism, neuro-ocular lesions.

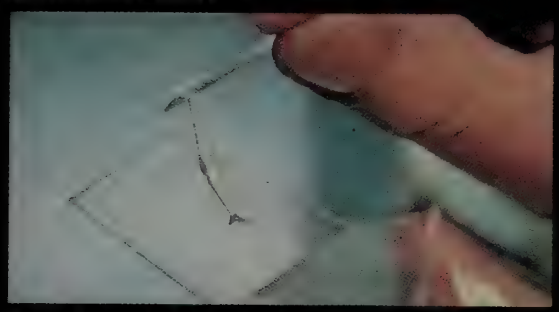
The following laboratory results may be altered by the use of oral contraceptives: increased sulfobromophthalein and other hepatic function tests, coagulation tests (increase in prothrombin, Factors VII, VIII, IX and X), thyroid function (increase in PBI and butanol extractable protein-bound iodine and decrease in T^3 values), metyrapone test, pregnanediol determination.

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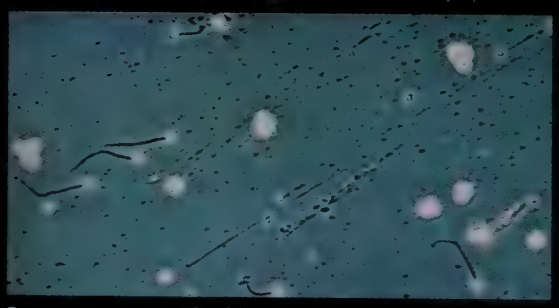
Here's why Norinyl-1 makes medical sense.

The effectiveness of Norinyl-1 as a low-dose oral contraceptive may be explained by its possible multiple action. In addition to its primary action of suppression of ovulation, Norinyl-1 may offer additional protective mechanisms.... (1) creation of a cervical mucus that may be hostile to sperm penetration, and (2) development of an endometrium that may be out of phase with nidation. These effects are illustrated below.

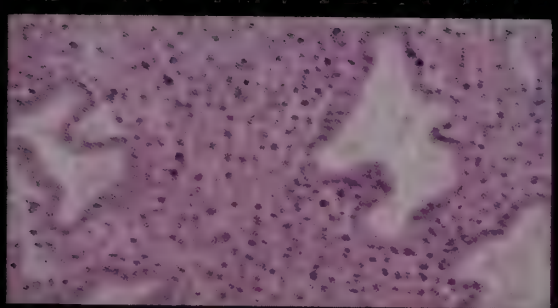
Untreated Patient



Cervical mucus at midcycle is usually thin and watery, with Spinnbarkeit (stretchability) of 15 to 20 cm.

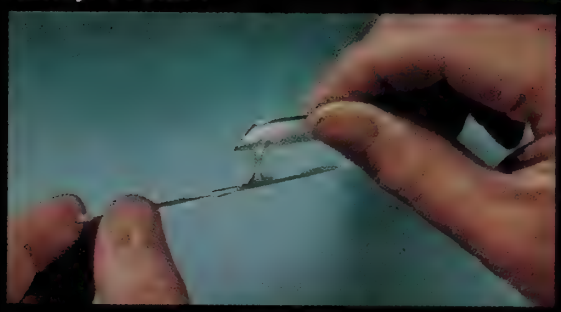


Spermatozoa appear healthy, active, freemoving.

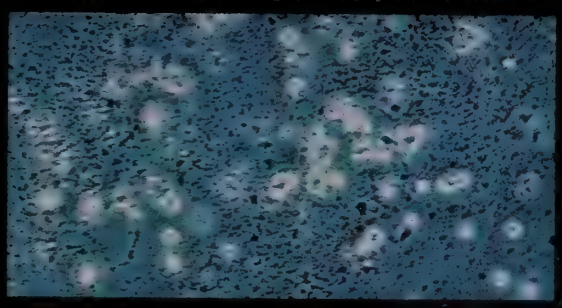


Endometrium of untreated patient is receptive to the fertilized ovum during secretory phase.

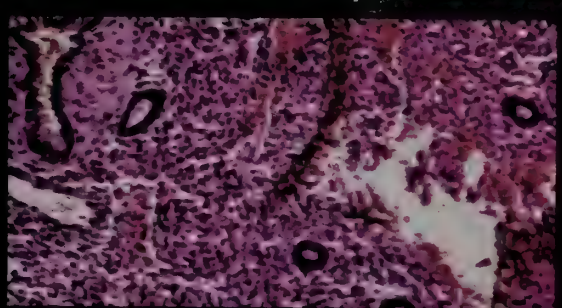
Norinyl-1 Patient



Cervical mucus at midcycle is scanty, viscous—with Spinnbarkeit of 1 cm. or less.



Immobile spermatozoa as they appear in cervical mucus taken from patient treated with Norinyl-1.



Norethindrone in Norinyl-1 accelerates secretory phase, suppresses glandular and vascular development.

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Turn page for contraindications, precautions and side effects

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Clinical Path Conference

Abdominal Mass and Acute Leukemia

Dr. Robert L. Strom:*

A 56-YEAR-OLD WHITE female was admitted to Hennepin County General Hospital in early March 1965 complaining of weakness and abdominal pain. There was a history of subtotal hysterectomy for carcinoma of the uterus twelve years previously. A diagnosis of carcinoma of the cervix had been made two years prior to admission, and the patient was hospitalized and treated with external radiation and radium implants.

Two months after completion of her therapy she was hospitalized because of cough, fever, and diarrhea. A chest x-ray revealed bilateral pulmonary infiltrations, suggestive of pneumonia. At this time abnormal hematologic findings were first noted. The patient's hemoglobin was 10 grams %, her white blood cell count 1100 per cu. mm. and her platelet count 101,000 per cu. mm. She was treated with 6-Mercaptopurine, Prednisone, and Erythromycin and made an uneventful recovery.

After an interval of six months the patient was again admitted because of recurrent leukopenia and anemia. Her hemogram included a hemoglobin of 7.5 grams %, a white blood cell count of 1200 per cu. mm. with a differential count showing 81% paramyeloblasts. A platelet count was 52,000 per cu. mm. and a reticulocyte count was 3.6%. Her therapy consisted of a transfusion of whole blood, Methotrexate 5 mg. every other day and Prednisone 10 mg. daily.

The patient was again hospitalized three weeks later because of recurrence of anemia. Acute perineal ulceration had developed. Over a 30-day period a number of drugs were administered, including Vincristine, 6-Mercaptopurine, Prednisone, and Methotrexate. Her hemogram remained essentially unchanged except for a fall in the platelet count to 13,000 per cu. mm. She was discharged on Prednisone 40 mg. daily with oral penicillin.

A little later she was readmitted to Hennepin County General Hospital in a moribund state. On examination her blood pressure was 50/0, temperature 102.4°F., pulse 140 per minute, respiratory rate 40 per minute. She appeared acutely ill and was slightly jaundiced. The heart and lungs were normal to examination. The abdomen was acutely tender, especially to the right of the midline. A large mass was felt extending to the pelvis in the right hemiabdomen. Bowel sounds were absent. The perineal ulcerations were again present.

Laboratory Studies

Laboratory studies included a hemoglobin of 8.9 grams %, a white blood cell count of 650 per cu. mm. with neutrophils 26%, lymphocytes 54%, and paramyeloblasts 18%. A platelet count was less than 10,000 per cu. mm. The prothrombin time was 21.7 seconds with a control of 12.6 seconds.

The following blood chemistries were obtained. Blood glucose 186 mg.%, BUN 87 mg.%, serum sodium 125 mEq/L, potassium 3.9 mEq/L, CO_2 combining power 11 mEq/L and

*Associate Pathologist, Hennepin County General Hospital.

chloride 87 mEq/L. A total serum bilirubin was 4.8 mg.% with a 3 mg.% direct reacting fraction. The thymol turbidity was less than 1 unit and a cephalin flocculation was 4+ in 48 hours. The alkaline phosphatase was 11 KA units, a serum creatinine 5.6 mg.%, and a serum uric acid was 11.9 mg.%.

A chest roentogenogram was normal. An upright film of the abdomen revealed a "moderate amount of gas in the stomach."

The patient's treatment included intravenous hydrocortisone, digitalis, Kanamycin, vasopressor, and packed red blood cells. She expired acutely four hours after admission.

Clinical Discussion

Dr. Robert Green:*

In reviewing this protocol it appears to be easily divided into two parts. Initially, I would like to discuss her course, diagnosis, and management before she came to Hennepin County General Hospital, and secondly, her brief, acute terminal course.

In reviewing her past history, she appears to have had two malignancies, the first dating back 12 years, when she had carcinoma of the endometrium, followed by a two-year history of carcinoma of the cervix. Then she was hospitalized at another institution for what appeared to be an acute pneumonia which responded to therapy. At that time she was first diagnosed as having a leukemia manifested by leukopenia, mild thrombocytopenia, and abnormal cell morphology. It does not actually say in the protocol that a diagnosis of leukemia was made; however, she was treated with Prednisone and 6-Mercaptopurine, which are appropriate therapy for leukemia. She apparently made a satisfactory response to this therapy since there was a six-month interval before her next hospitalization. A blood smear on that next admission showed 81% paramyeloblasts, which confirms our suspicion that she did indeed have acute leukemia. Following several transfusions a course of Methotrexate was initiated and after a three-week interval she was started on a combination of antimetabolites, including Vincristine 6-Mercaptopurine and steroids. She was then discharged on a small dose of Prednisone and penicillin.

Shortly thereafter, she returned to this hospital for a brief terminal course, complaining of abdominal pain. At this time she was in shock and febrile. An abdominal mass was found and perineal ulceration was described. There were various abnormalities in her blood chemistries, all of which suggested a preterminal state. Then, despite intensive treatment, she expired.

Uterine Cancer and Leukemia

The only comment I have about her initial course is that the advent of her cervical carcinoma is certainly testimony against the performance of subtotal hysterectomy. One must not overlook the possibility of the presence of a residual cervical stump even in those individuals who state that they have had a total hysterectomy. We do not have the details of her irradiation; however, I assume she had the conventional therapy for cancer of the cervix with multiple portals delivering 3000 to 3500 roentgens to the cervix plus radium implants. I think it is safe to say that her cervical cancer irradiation sufficiently preceded the development of her leukemia to have very little, if anything, to do with it.

*Attending physician Hennepin County General Hospital.

Induction Therapy in Acute Leukemia

At this point I would like to comment on the type of leukemia and the mode of therapy. I reviewed the initial bone marrow sections and smears from 1965. As the marrow smears show a high percentage of blasts, I think one can readily make the diagnosis of acute leukemia. In studying the marrow, it appears to me that this was probably an acute myelogenous leukemia The acute leukemias are sometimes very difficult to classify on the study of the peripheral blood or bone marrow. In this one I tried to convince myself that I could see Auer rods. The implications of a diagnosis of myelogenous or lymphatic leukemia are a little different, even in adults. At that time, she was treated with 6-Mercaptopurine and Prednisone.

In reading the literature you may be somewhat confused by the various percentages of remissions induced in leukemia. Most of the good remissions reported refer entirely to acute lymphatic leukemia in children. This is an entirely different situation from acute myelogenous leukemia in either children or adults. In acute lymphocytic leukemia in children with appropriate induction therapy, we can expect an 80 to 90% remission rate. In adults with acute leukemia and particularly acute myelogenous leukemia, we are doing well if we can achieve a 10% remission rate. Most of the literature now indicates that induction therapy in acute myelocytic leukemia in adults still gives only about a 10% remission rate. This lady must have fallen into the 10%, because she had a very satisfactory remission induced by this combination of drugs. At least we don't hear anything more of her for another six months, and if she survived six months after initiation of treatment, I think one would have to consider this a good result. Most hematologists have seen patients who have responded to 6-Mercaptopurine and Prednisone, but the number of these patients is disappointingly few.

The next admission is occasioned by anemia and leukopenia. To comment on leukopenia and acute leukemia, in general: the prognosis is better if the leukocyte count is low. Patients with acute leukemia and high leukocyte counts have a generally poorer prognosis.

A study of the peripheral blood in this patient showed 81% paramyeloblasts. Often the clinical course in acute leukemia does not parallel the blast percentage in the peripheral blood and bone marrow. We see some patients with 25% blasts in the marrow running a very malignant course. On the other hand, we see patients with 90% blast forms who do not run such a malignant course.

On her second admission the patient was transfused and given Methotrexate. Now Methotrexate induction in acute myelocytic or lymphocytic leukemia in adults is, generally speaking, not very effective. Our current thinking is that Methotrexate and 6-Mercaptopurine are poor inducers but good drugs for sustaining remission. Here Methotrexate was given in rather unusual dosages, 5 mg. every other day, and we do not know for how long. There is now a regimen described by Huguley using Methotrexate for induction.[1] In this regimen a large dosage of Methotrexate is given orally: 2½ mg. every six hours for 20 doses. This is a very large dose, from which one can anticipate severe toxicity, but Huguley has succeeded in inducing some remissions in this way. I might just state that if the patient had had 5 mg. of Methotrexate intravenously or intramuscularly every other day rather than orally, we might have had a better prospect for remission. There are some reports that

Methotrexate intravenously rather than orally is more effective in inducing a remission.

VAMP Program

Then some three weeks later the patient returned; apparently this larger dose of Methotrexate was unsuccessful. At this point she was put on the Vincristine, 6-Mercaptopurine, Prednisone and Methotrexate program which most of you know is commonly called the VAMP Program, consisting of four drugs. The "V" stands for Vincristine, usually given in a dose of 25 micrograms per kilogram, generally resulting in a weekly dosage of 2 mg. intravenously. The "A" stands for Amethopterin or Methotrexate, given in a dosage of 2.5 mg. per day by mouth. The "M" stands for 6-Mercaptopurine, given in a dosage of 100 mg. per day by mouth. The "P" represents Prednisone, given in a dosage of 60 to 80 mg. per day. There are some variations of this program, such as one called "Vampette" which includes smaller doses; and there are other variations from the standard VAMP schedule. We have used VAMP here at Hennepin County General Hospital in a number of cases of acute leukemia with uniformly poor results; I myself have induced a remission in only one patient with acute myelogenous leukemia with this VAMP schedule. Many people are giving up this program for induction in acute leukemia in adults. However, there is apparently no better program than VAMP for inducing remission. Dameshek[2] has published a series in which he claims equal clinical results with 6-Mercaptopurine and Prednisone; but no one else can duplicate his results. The induction rate with VAMP, published from miscellaneous sources, is 40% remissions of varying duration in adults with acute myelocytic leukemia. I am sure this is optimistic.

I am making the point of differentiating induction from treatment or maintenance: a drug used for induction is not used for maintenance, and conversely. There are two new drugs not as yet available which may improve induction treatment. The first is Cytosine arabinoside, reported to induce remission in approximately 25% of adults with acute myelogenous leukemia. The other drug is Daunomycin or l-Asparaginase, an extremely toxic drug; but there has been some success in induction of remission in acute leukemia with this agent. In general, the second and third attempts at remission in acute leukemia are unsuccessful. We have our best chance of inducing a remission on the initial attempt.

The dosage of 5 mg. of Prednisone a day on which the patient was discharged is a drop in the bucket. If one is going to use Prednisone to induce a remission in adults with acute leukemia, one must use a large dosage, such as, a minimum of 60 mg. of Prednisone a day. There was a big scare about the usage of Prednisone by Wintrobe a few years ago, but I think most hematologists feel that high-dose Prednisone is the cornerstone of any treatment of acute leukemia in adults.

On her final admission, the patient came in with what I assumed to be septicemic shock. She had an abdominal mass with no bowel sounds and the perineal ulceration previously described. She was markedly leukopenic at this time, and it is not clear whether the VAMP therapy had reduced the blast count significantly. There was once again a thrombocytopenia, and the prothrombin time was elevated.

Steroid-Induced Diabetes

I would like to comment briefly on the presence of hyperglycemia. On none

of the previous admissions was hyperglycemia mentioned, and it is quite possible that this lady had steroid-induced diabetes. Prednisone therapy over a long period of time may have been at least partially responsible for this elevated blood sugar. She had a BUN of 87 mg% and markedly elevated creatinine suggesting that there was something adverse going on with the kidneys, tending to elevate the blood sugar.

Addisonian Crisis

She was hyponatremic and hypokalemic, and I wondered if she might have Addison's disease induced by exogenous steroid therapy. She had been discharged on 40 mg. of Prednisone a day; but we do not know whether she took it or not. It is possible that she may have had acute adrenal insufficiency, but I should think that her potassium would be somewhat higher, particularly in view of the renal insufficiency.

We find also that she was acidotic and moderately jaundiced. Most of the bilirubin elevation is direct-reacting or conjugated bilirubin, which suggests that this was obstructive jaundice rather than a hemolytic anemia related to her leukemia. Her alkaline phosphatase was not markedly elevated, and this would suggest that she did not have much of an obstructive component to her jaundice. The elevated uric acid might also be mentioned here. In acute leukemias of almost any form, the uric acid may be markedly elevated. Her basic disease plus her renal insufficiency adequately accounts for the elevated uric acid.

On her final admission, she had nothing in her lung fields to account for her fever. She had an abdominal mass, however, and I wonder if we could now review the x-rays to see if we can account for this intra-abdominal process?

Radiological Findings

Dr. S. H. Tsai:*

The chest x-ray is normal. An upright study of the abdomen is available, and we can see the upper margin of the abdominal mass adjacent to the inferior surface of the liver (Figure 1). But I cannot see the inferior or medial aspect of the mass. There is a dilated loop of small bowel in the mid-abdomen. The spleen is not particularly enlarged, and no free air is noted under the diaphragm. One has the general impression of a kidney outline on the right; however, this is quite indistinct. The exact relationship between the mass and the right kidney cannot be ascertained with certainty.

Discussion

Dr. Green:

Perineal ulceration appears on two occasions in the protocol, and I am not sure why. These ulcers in the perineum are probably the same sort of ulceration that occurs in the mouths of patients with leukemia and agranulocytosis which this lady manifested in the latter part of her course after her drug therapy.

Differential Diagnosis of Abdominal Mass in the Right Upper Quadrant

This reduces us to the differential diagnosis of her abdominal mass. What did this mass in the right side of the abdomen actually represent? And

*Chief of Radiology, Hennepin County General Hospital.

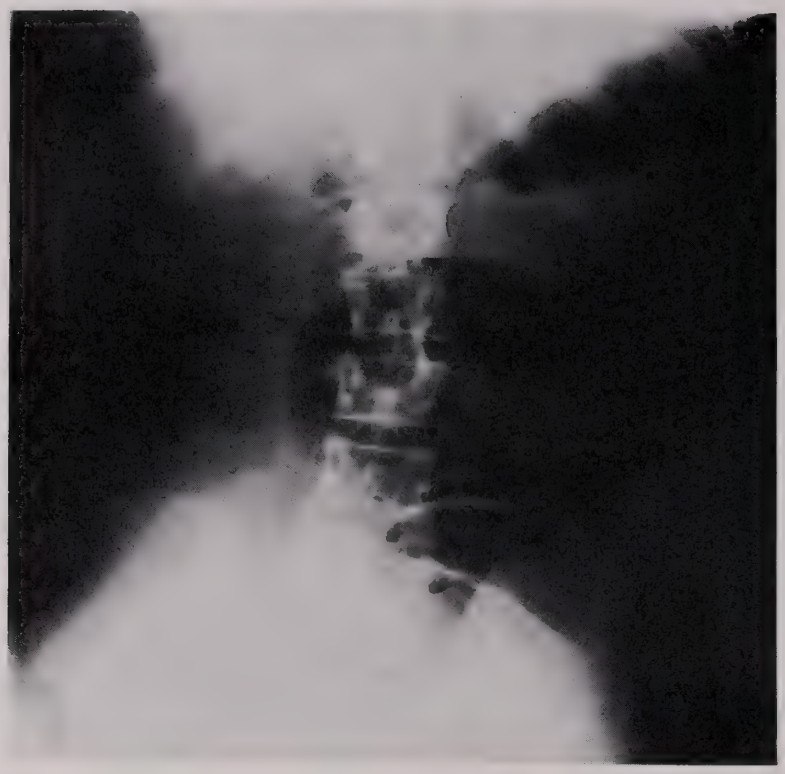


Fig. 1—Flat Plate of the Abdomen: An increased density is noted in the region of the right colon with an absence of bowel gas in the right hemi-abdomen.

how did it relate to her fever, shock and terminal course? There is nothing in the earlier portions of the protocol to indicate what this mass might be. We know that she was in grave condition because of her leukemia and the results of her treatment. Her tissue leukocyte count was decreased and she was on steroids which probably inhibited her response to infection.

Hepatic Enlargement

We could continue through a differential diagnosis of the right upper quadrant mass, and our initial thoughts might center about the liver since there was jaundice and an elevated prothrombin time. Leukemic involvement of the liver seldom produces this much hepatic enlargement. There must have been something complicating it, like congestive heart failure. She may have had serum-induced hepatitis from her previous admissions, but the evidence is insufficient. It is possible that with her leukemia and steroid therapy she had some sort of infra-hepatic or subhepatic abscess but we have no findings suggestive of this diagnosis on the chest x-rays. It is conceivable that she could have had metastatic cancer to the liver from one of her primary malignancies in the uterus, but there is little to suggest this, and her alkaline phosphatase was not markedly elevated.

Empyema of the Gallbladder

The gallbladder is in the right upper quadrant of the abdomen, and as she had abdominal pain and a tender mass, I assume that this could have been an

acute cholecystitis with empyema. However, in reviewing the films, she certainly had a large mass, the exact origin of which is not easy to ascertain.

Pancreatitis with Pseudocyst

I wonder if a serum amylase was done on this admission? That is the only other piece of laboratory information I would like to have. One would wonder if the abdominal mass could have represented a pancreatic pseudocyst or an ischemic portion of bowel.

The pancreas could be the source of the mass, since pancreatic pseudocysts develop after episodes of acute pancreatitis. An acute pancreatic cyst with hemorrhage into it can present as a right abdominal mass; however, it is more common to have the cystic masses present in the body or tail of the pancreas on the left. Such a cyst could cause an increase in bile duct pressure which would elevate the bilirubin. There is nothing much to suggest that the mass is coming out of the right kidney or from the retroperitoneal space.

Volvulus of the Right Colon

Another thing which might partially explain these findings would be some sort of catastrophe involving the right colon. This patient was undoubtedly emaciated and probably had a colon on a long mesentery which could have undergone a sudden volvulus with the development of an ischemic bowel and peritonitis. If she had a volvulus of her right colon, that could account for her pain, the electrolyte abnormalities, and her septic course with shock. To explain her terminal course, I would have to guess between some infectious process involving the gallbladder, a hemorrhagic pancreatitis, or some process such as a volvulus involving the right colon.

The management of her leukemia was apparently successful and a short remission was induced; but as so often happens, patients with leukemia die of infections. Since she had a prothrombin deficiency and a marked thrombocytopenia, an intra-abdominal hemorrhage or retroperitoneal hematoma would have to be considered. However, there was no mention of systemic purpura or hemorrhagic manifestations in the skin. Most patients with leukemia who die of hemorrhagic manifestations are bleeding everywhere, including their skin, nose and mucous membranes; but we have no evidence of that here. I would have to assume she died of a complication of her leukemia with infection and some process in one of the three organs giving rise to the intra-abdominal mass.

Clinical Diagnoses:

1. Acute myelogenous leukemia
2. Intra-abdominal abscess involving the gallbladder, pancreas or right colon
3. Septicemic shock

Pathology

Dr. Strom:

We were fortunate enough to be able to study the bone marrow slides from an outside institution taken on this patient in 1965 and early 1966. The section material from the bone marrow done early in 1965 appeared normocellu-

lar; however, the smears taken from this marrow showed increased numbers of primitive cells. In addition to the primitive blast cells, which numbered up to 5%, one noted a prominent left shift in the neutrophil series. The pathologist studying the material was probably faced with a familiar quandary; since there was no overgrowth of the hematopoietic elements in the bone marrow sections, but he was required to explain the ominous left shift in the neutrophil series. This initial marrow was interpreted as showing a striking left shift and neutrophilia.

The marrow study done in late 1965 shows a definite leukemia. The marrow sections are by this time totally overrun with myeloid elements, and I assume a definitive diagnosis of leukemia was made at that time. A smear from this study shows that nearly all the cells seen are blast cells and may be interpreted as paramyeloblasts. The cell nuclei are enlarged, rounded, and sometimes slightly indented, and they have a delicate chromatin network. Multiple nucleoli are frequently present in the nuclei. The cytoplasm of many of these blast cells is dark bluish grey, and some azure granules are noted. A few of these azure granules tend to line up, and one can convince oneself that Auer rods are seen in blast cells in rare instances. In addition, one sees vacuoles in the cytoplasm and sometimes overlying the nucleus, which are clear and sometimes slightly pink in color. I can understand why the hematologist called these cells paramyeloblasts, because in many ways they are not typical myeloblasts. One would have to think of some differentiation towards monocytes as well as granulocytes. I would like to classify this leukemia as being in the myelomonocytic group. One hematologist might prefer to call this the Naegeli type of monocytic leukemia, whereas another might consider it a variant of acute myelogenous leukemia with a terminal release of primitive reticulum cells. Not infrequently in the latter stages of chronic myelogenous leukemia in relapse one sees elevated leukocyte counts with increased numbers of primitive reticulum cells and young myeloid elements. Typical cellular elements from the peripheral blood as seen in late 1965 are shown in Figure 2. I was intrigued by the vacuolation in the blast forms, and I feel that if we had had some unstained material, a Sudan Black B stain of the blast forms might have been helpful in giving some insight into the direction in which the cell forms were differentiating. On the marrow smear taken in early 1966, 90 to 95% of the cells in the marrow were blast cells, thus confirming the diagnosis of acute leukemia (Figure 3). The number of developing red cells in the marrow was strikingly reduced. A paucity of mature cells in the neutrophil series was obvious.

Post-Mortem Examination

The pathologist naturally likes to be able to verify the diagnosis of acute leukemia at autopsy; but sometimes we have difficulty doing this. The hematopoietic organs held our initial interest during the post-mortem examination. The liver weighed only 1100 grams and was not particularly enlarged. The Kupfer cells in the hepatic sinusoids were seen to have ingested hemosiderin and foreign material, but these did not appear to be part of a leukemic process. The reason for the jaundice was relatively obscure since there was no evidence of common-duct obstruction. The lymph nodes were not enlarged either in the abdomen or in other areas of the body. The spleen was very small, weighing only 210 grams. We do not expect the spleen to be particularly

enlarged in cases of acute leukemia, so we must go to our section material to try to confirm the presence or absence of leukemic involvement of the spleen. There was some loss of definition between the malpighian corpuscles and red pulp; however, the lymphoid cells tended to aggregate around the cen-

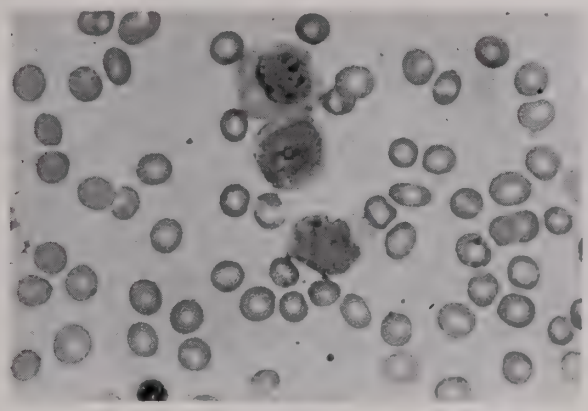


Fig. 2—Peripheral Blood. 100X: Two paramyeloblasts with clear and pink vacuoles are seen in the central portion of the field; a neutrophil myelocyte is seen at the top of the field.

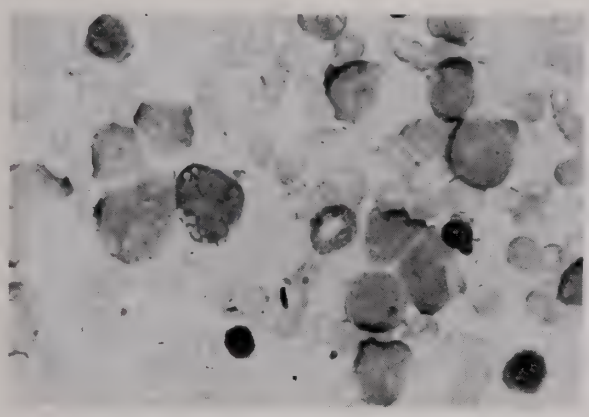


Fig. 3—Bone Marrow Smear. 100X: A preponderance of paramyeloblasts is seen in this view of the marrow, with only occasional normoblasts.

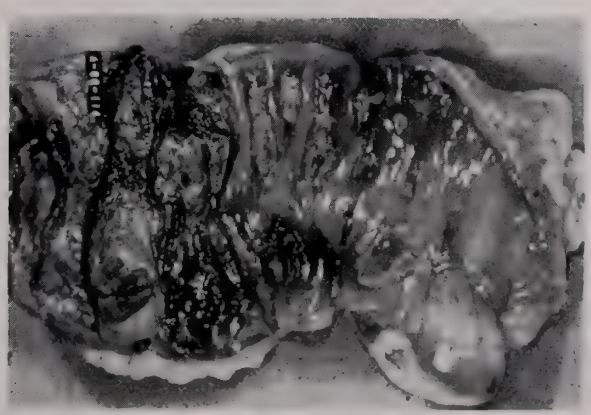


Fig. 4—Right Colon Mass when opened, showing ulceration, edema, and necrosis.

tral artery of the malpighian corpuscles, and the background reticulum was limited to the red pulp. An increased deposition of hemosiderin was seen in the red pulp; also some primitive reticulum and myeloid elements were present. Occasional megakaryocytes were observed, suggesting some myeloid metaplasia of the spleen.

Acute Colitis and Peritonitis

The gallbladder and pancreas were normal. We then focused our attention on the abdominal mass involving the right colon. As pictured in Figure 4, one can see that it was involved in a bizarre process characterized by thickening, edema, hemorrhage, and necrosis. When opened, the mucosa of the ascending colon and cecum showed extensive areas of ulceration with greenish discoloration suggestive of acute staphylococcal enterocolitis. Irregular mucosal projections extended into the lumen of the bowel, and I wondered on initial examination if this represented tumor or leukemic infiltration. A frozen section taken from one of the projections suggested only edema and necrosis without primary malignant infiltration (Figure 5). I imagine that Dr. Tsai is somewhat relieved that he did not have to evaluate a barium enema on this patient. As there was no evidence of mechanical volvulus or twisting associated with this bowel lesion, I can only assume that this was secondary to agranulocytosis with

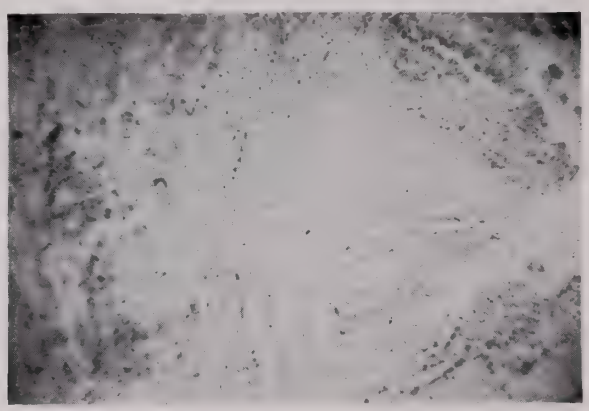


Fig. 5—Mucosa of Right Colon 40X showing necrosis, edema, and lack of tissue cellular response.

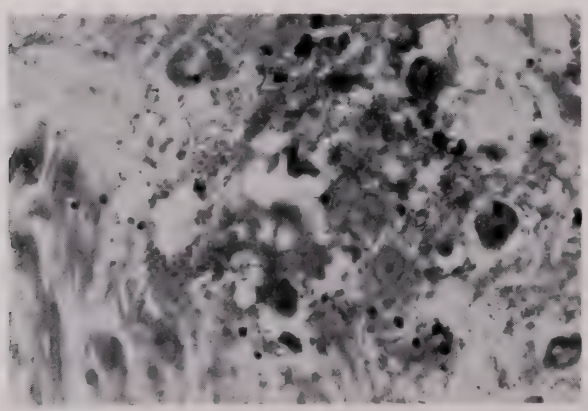


Fig. 6—Tissue Gram Stain 100X: Proliferating gram-negative rods are seen in the bowel muscularis not eliciting a cellular response.

suppression of the leukocytes in the tissue compartment. Much of the bowel wall was non-viable and there was evidence of an early peritonitis in the serosa. Colonies of proliferating gram-negative bacteria were seen in the external layers of the muscularis of the bowel (Figure 6). I can only assume that the leukocytic response in the tissue compartment was so inadequate, due to the therapy, that this unfortunate lady's bowel flora multiplied and penetrated the bowel wall, resulting in a systemic septicemia. Post-mortem blood culture studies revealed Paracolobactrum and Escherichia coli species, commonly isolated as part of the normal bowel flora, which under these circumstances had become pathogenic. There was evidence of associated vasculitis and pylephlebitis of the mesentery; but neither hepatic nor subhepatic abscess had supervened.

On examination of the adrenal glands one could see atrophy induced by exogenous steroid dosage, but there was no evidence of adrenal hemorrhage or Waterhouse-Friderichsen syndrome. Adrenal hemorrhage commonly complicates a gram-negative septicemia. I would not be in a position to comment on whether clinical adrenal insufficiency was present terminally, but it does not appear to be likely.

Pathological diagnosis:

1. Acute myelomonocytic leukemia (Naegeli type)
2. Acute colitis of the right colon with peritonitis
3. Terminal gram-negative sepsis due to bowel flora

Closing Comments

Dr. Strom:

Dr. Green, would you comment on the indications for surgical exploration in patients with acute leukemia? Certainly, surgical exploration did not appear to be indicated in a woman in this state of extremis; however, are there any indications for surgical intervention in patients with acute leukemia?

Dr. Green:

Obviously each case has to be individualized and most adults with acute leukemia are very poor surgical risks. In a case such as this with bacteremic shock, the patient was obviously no surgical candidate.

I would just like to emphasize this problem of the association of steroids and infection. We can divide the granulocyte pool into the circulating granulocyte pool, the marrow granulocyte pool, and the tissue granulocyte pool. Cartwright[3,4] has pointed out that the neutrophils can exchange from the marrow pool to the circulating pool, and the marginal leukocytes are part of the circulating pool. There are many more leukocytes marginated than are circulating, but with steroid therapy the circulating granulocyte pool increases. The administration of steroids will elevate the leukocyte count, since increased numbers of granulocytes are circulating. With steroid therapy there is a block and the neutrophils are not released freely to the tissues from the circulating pool. The granulocytes simply do not get to the tissues where they are needed.

A Medical Student:

Do people with solid tumors have a higher incidence of developing blood dyscrasias?

Dr. Green:

No, I do not think so. There is a higher incidence of cancer in patients with

leukemia than in non-leukemic patients, but the reason for this is obscure.

Dr. Strom:

I think the timing of the onset of leukemia in this case is somewhat interesting, however, because we have seen cases of leukemia following radiation for cancer of other types. I can remember two cases of acute leukemia that developed within six months after irradiation following a mastectomy for carcinoma of the breast. One might speculate in this case whether the onset of leukemia could be related to the irradiation of the cervix. There was no evidence of residual cancer in the cervical stump.

Dr. Green:

The only problem about that is that in the Hiroshima-Nagasaki victims who received a lot more total body irradiation, the interval between exposure and onset of their acute leukemias peaked out at approximately 18 months following exposure. Cases of acute leukemia began developing by nine to 10 months, but the peak incidence came much later. The time interval here appears to have been just a few months after her cervical irradiation.

Dr. Tsari:

I think also that a two-month interval is too short to incriminate irradiation as the cause of the acute leukemia. We do not know the stimulus that triggers acute leukemia.

Robert L. Strom, M.D.*
Hennepin County General Hospital

*Associate Pathologist.
References may be obtained from the author.

Hedblom's Syndrome

This syndrome consists of an acute primary myositis of one or both leaves of the diaphragm with inspiratory pain, lower chest immobility, and upper abdominal pains without other signs of abdominal pathology. Joannides in 1935 described the lesion and suggested the eponymic term in honor of the thoracic surgeon Carl A. Hedblom.

Clinically, the onset may be sudden with a chill. The ipsilateral lower costal pain is frequently referred to the shoulder area. Fluoroscopic observations or roentgenographic studies reveal a gradual diminution and almost complete flattening of the normal dome of the diaphragm. Pathologically, there is swelling of the muscle fibers with leukocytic infiltration into the tissues. The pathology may be limited to the muscle bundles or may extend to the serous surfaces, the pleura, and the peritoneum. No constant or specific causative organisms have been recognized. The high incidence of trichiniasis of the diaphragm is well recorded but has not been related etiologically to this syndrome.

Differential diagnosis should exclude eventration of the diaphragm, spontaneous pneumothorax, acute surgical conditions in the abdomen, and epidemic diaphragmatic pleurodynia. Consideration must also be given to spontaneous pneumoperitoneum, irritation of the phrenic nerve trunk associated with mediastinal pathology, and pulmonary atelectasis. The condition is self-limited but has a tendency to recur. Broad-spectrum antibiotic therapy may be useful.

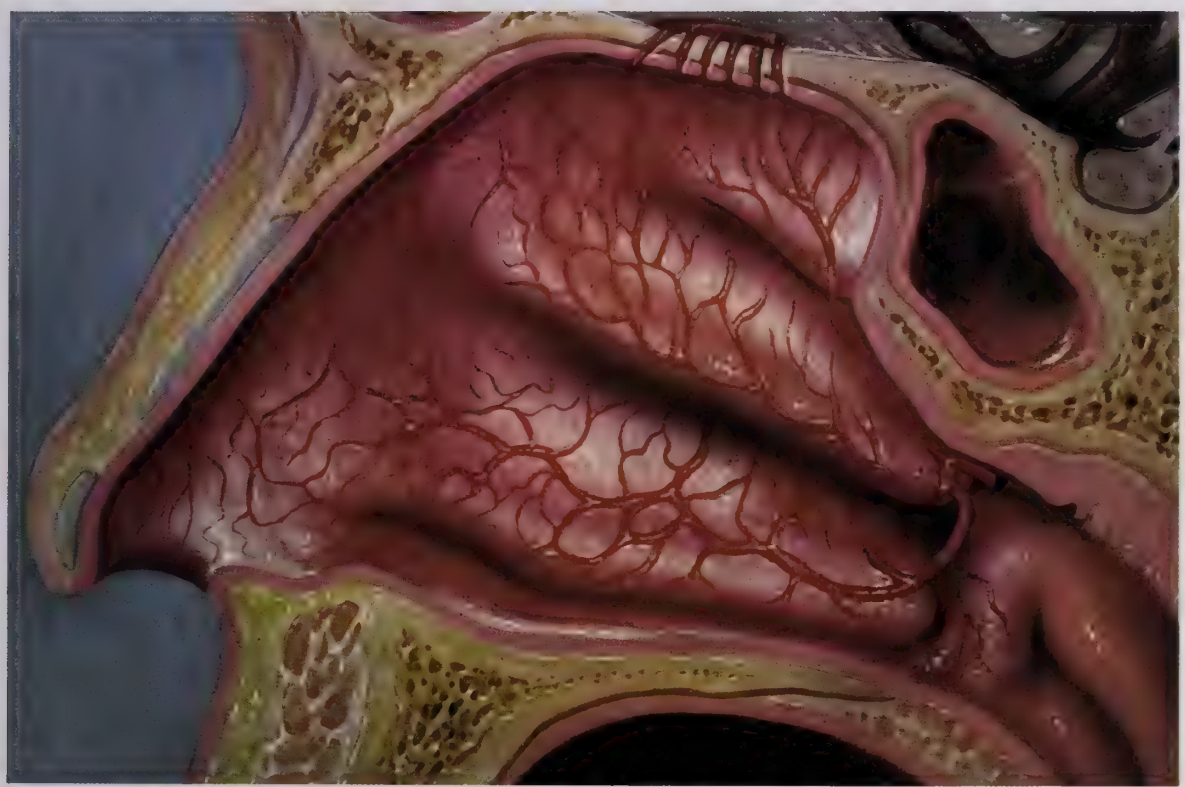
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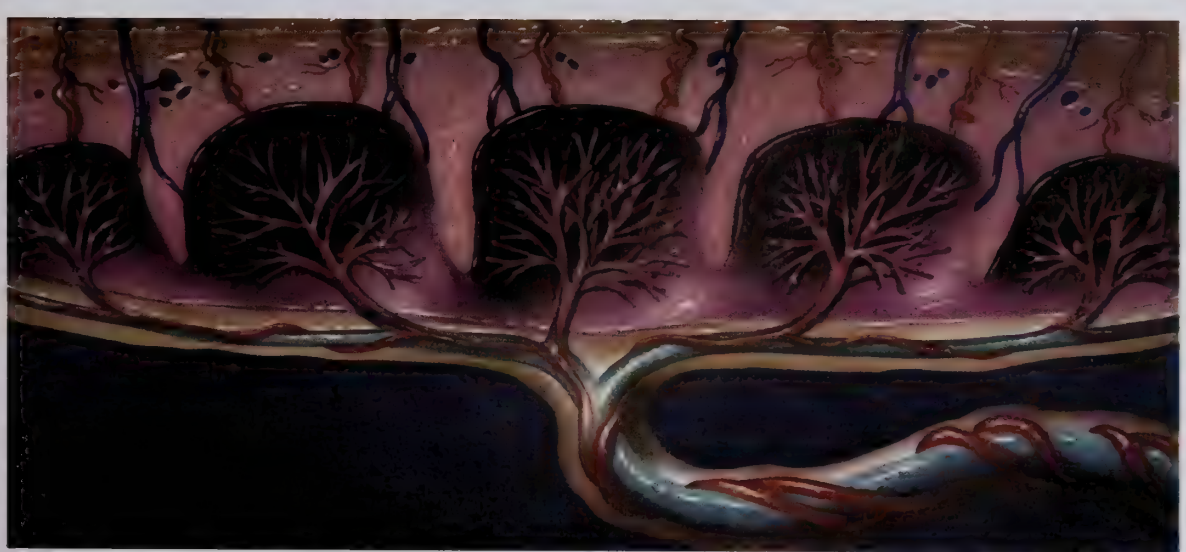
A man who is a genius and doesn't know it probably isn't.—Lec

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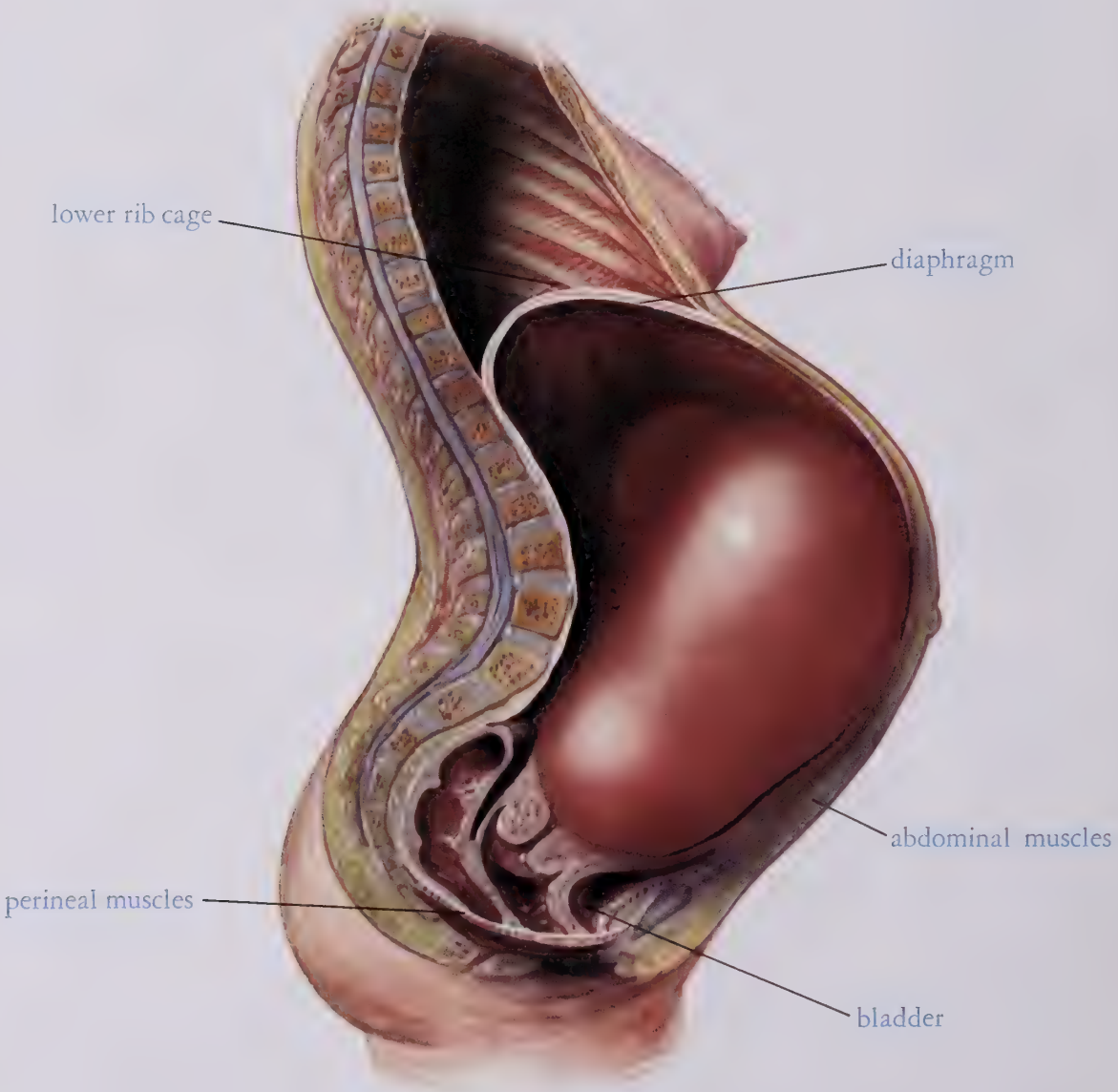
the cold in pregnancy

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Since pregnancy and the common cold are both ubiquitous, it is not surprising that they often occur at the same time in the same patient. Incidence figures are hard to come by, but the chances are very good that any given pregnant woman will have a cold at some time during the nine months of her gestation. When she does, she will tell you that it is the worst cold she ever had. It seems to last longer and the symptoms are more distressing than they are in the non-pregnant.

For purposes of this discussion, the common cold is considered to be the well-known symptom complex which includes sore throat, stuffy nose, and a cough. Febrile states or extension of the disease process into the lower respiratory tree are not part of the common cold and will not be included in this discussion.

The clinical picture of a cold in pregnancy can be confused by a long-known physiological phenome-



non. Kiesselbach's area in the nose (on the anterior part of the nasal septum above the intermaxillary bone) becomes engorged, apparently due to hyperemia induced by the increased estrogen level which accompanies pregnancy. The amount of congestion can vary in degree from woman to woman. Some have very little congestion, others will have occasional nosebleeds from this area, still others will have symptomatic congestion to the degree that they will complain of having a "chronic" or constant cold.

Less well recognized is the occurrence of this type of hyperemia in any part of the nasopharyngeal mucosa, again in varying degree. Such swelling often produces a postnasal drip which, the patient will state, is present only when she is pregnant. Patients who do not have symptomatic congestion ordinarily, will find that when they do get a cold, the symptoms last much longer than those of a cold usually do. Occasionally, this hyperemia is responsible for closure of the medial end of the Eustachian tube; such patients will complain of "plugging" of the ears. Inspection of the ear drum will show a depression which confirms the presence of Eustachian closure rather than wax in the canal which is the patient's diagnosis. Symptoms related to this physiological congestion are more apt to occur in heavier smokers or those who have a history of allergic rhinitis, just as are the symptoms of the common cold. And when the cold does occur in pregnancy, the symptoms are worse because of the underlying congestion.

The pregnant woman with a cold is miserable for other reasons, dependent somewhat on her parity and the length of her gestation. As parity increases, so also does the relaxation of the abdominal and perineal musculature. The uterus, lying against a slack abdominal wall, and bearing down on relaxed perineal muscles, acts like a piston when the patient coughs, sneezes, or even blows her nose, pushing down on the bladder. Stress incontinence during colds is almost the rule.

As the length of gestation increases, so does the size of the uterus. As it grows, it pushes the abdominal contents above it and elevates the diaphragm. This results eventually in a lateral displacement of the lower rib cage, often to a point at which the patient will complain of soreness in this area. If such a

(Concluded on following page)

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patient has a cold, the coughing and sneezing will exaggerate this soreness. The diaphragmatic restriction caused by the enlarging uterus also makes breathing more difficult, particularly when the patient lies down. A cold compounds this difficulty.

Treating a cold in pregnancy requires two additional considerations. The patient should be told that the symptoms may last longer lest she become discouraged, and she should be reassured that the treatment will not damage the fetus. Although there are still some women who seem blissfully ignorant regarding matters of health (and these need to be cautioned not to take medication recommended by friends), most of our maternity patients are aware of the thalidomide tragedy. These women need constant reassurance that the symptoms of a cold can be treated, and that the medication is safe. Fortunately, many of the drugs which are of benefit have been in use long enough and widely enough so that such a statement can be offered. Occasionally one encounters a patient who is so anxious to avoid medication that she is extremely reluctant to take anything at all. Since cold is self-limited, it seems reasonable enough to give such a patient the choice and not to force drugs on her if she is obviously afraid of taking them.

The most distressing symptom of the common cold is the nasal congestion. This can be mitigated by the use of a decongestant which will help reduce the postnasal drip and the coughing caused by it. The kind of a cough which is described as a "tickling" in the throat and which is apt to occur when the patient goes to bed is usually due to nasopharyngeal congestion rather than inflammation in the lower respiratory tract.

There are many cough mixtures available. Most contain an antihistamine, a decongestant, and a cough "suppressant." Should cough suppression be desirable, it is important to remember not to use both a decongestant tablet and such a cough mixture as the patient would be getting a double dose of the decongestant. With some patients, the placebo effect of a cough syrup may be important and a liquid preparation might be substituted for an oral tablet.

For a sore throat, candy drops or lozenges at frequent intervals are soothing. It is not only unnecessary but unwise to use antibiotic lozenges or drops. The use of antibiotics in an uncomplicated cold is contraindicated and should be scrupulously avoided.

In summary, a cold in pregnancy is more severe and longer lasting. The treatment of the symptoms with local and systemic decongestants will make the patient more comfortable.

Apparently the cold is so common in pregnancy that it has received very little attention in the literature. References are almost non-existent and the few which are available add little to the common knowledge, are out-dated, or are not helpful. Thus the usual bibliography is not appended.



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Grand Rounds

Stevens-Johnson Syndrome

M. THOMAS STILLMAN, M.D.
Medical Resident

STEVENS-JOHNSON syndrome has been considered an "acute inflammatory systemic disease producing a variety of clinical patterns."[1] Although the clinical manifestations are well recognized, the pathogenesis and presumed etiology remain as medical mysteries. The literature is filled with case reports of this syndrome whose causal role could well be challenged.

Classification

The classification of Stevens-Johnson syndrome has met with much uncertainty and confusion. Alexander and Cope[2] reviewed the historical development of this syndrome.

Skin Lesions

In 1860, Hebra reported on an acute illness characterized by the presence of a polymorphic skin eruption. He called this illness "erythema multiforme exudativum," and the skin lesions consisted of irregularly shaped areas of erythema, papules, vesicles, and bullae. In 1862, Bazin noted the presence of constitutional symptoms and oral lesions with this skin eruption.

Oral and Ophthalmic Skin Lesions

The oral lesions were better described in 1882 by Quinquaud. In 1896 von During described in detail the presence of conjunctivitis. The syndrome as we picture it today was described by Stevens and Johnson[3] in 1922 when they reported two cases of an eruptive fever associated with stomatitis and ocular complications. In 1951, Ashby and Lazar[4] suggested the term "erythema multiforme exudativum major" to distinguish the more severe variants

*Presented as a Medical Grand Rounds at Hennepin County General Hospital, September 19, 1967.

from the "minor" or mild forms as originally described by Hebra. The nomenclature has been very confusing, and this is reflected by the number of synonyms used since Stevens and Johnson's description in 1922. Some of the synonyms include: erythema multiforme pluriorificiales, mucocutaneous fever, eruptive fever with stomatitis and ophthalmia, ectodermose erosive pluriorificelle, the triple complex, mucosal respiratory syndrome, dermatostomatitis, erythema bullosum malignans pulriorificial type, and erythema polyforme bulleux. One could say that we are probably dealing with degrees of intensity in a spectrum of clinical reactions that vary from mild to fatal manifestations.

Clinical Manifestations

The general clinical manifestations of this syndrome have been well described.[5-11] The prodromal period varies from one to fourteen days and is characterized by such general symptoms as fever, cough, malaise, coryza, sore throat, myalgia, chest pain, and arthralgia in varying combinations. This is followed by the skin and mucous membrane eruption together with various visceral involvements.

Skin

Initially, rapidly developing skin lesions may be the only manifestation. The rash is usually symmetrical and starts on the extensor surfaces of the hands, arms, and feet. The entire body may become involved, but the scalp is usually spared. The lesions start as erythematous areas that may become papular, vesicular or even bullous. Macules may show a fading center, or hemorrhage may occur into affected areas, thus giving rise to the so-called target, iris, or bull's-eye lesion. If the disease progresses, erosion, ulceration, and scaling may occur, leaving areas of the body stripped of epidermis.

Mucous Membrane

Characteristically the mucous membranes are equally involved with the skin. The most commonly involved areas are the nose, mouth, and eyes, but the genitalia and anus may also develop lesions. The buccal mucosa may become fiery red with scattered petechial hemorrhages. There may be marked swelling and intense pain within the mouth. Vesicles develop that soon rupture, leaving ulcers oozing with bloody serum. These ulcers then darken with clots or are covered with a typical gray-white pseudomembrane. The lips are often covered with a bloody crust, and eating and drinking becomes very difficult. The pharynx and esophagus may become involved and the patient often spits up blood-stained pus.

Ocular

The ocular manifestations of this syndrome are common but highly variable. Howard[9] reviewed the eye manifestations in detail. There is no pathognomonic eye lesion, and mild conjunctival injection may be the only finding. Conjunctivitis is common and the discharge is catarrhal, purulent, or pseudomembranous. The lids may become swollen and ulcerated, and iritis, iridocyclitis and panophthalmitis may develop. Corneal involvement with opacification or pannus formation leads to partial or total blindness in the involved eye. In chronic cases, photophobia, blepharospasm, persistent mucinous discharge, and immobilization of the globe are possible complications.

Since the advent of sulfonamides and antimicrobials, severe ocular damage is less frequent. In Howard's study of 61 patients, 10 developed severe ocular signs, two of whom were left with visual loss.

Sex and Age

The genitalia may be involved in either sex. In the male, penile and scrotal ulcerations occur and in the female vulvovaginitis. In both sexes, a urethritis occasionally occurs, associated with a thin, purulent discharge. The anal mucocutaneous junction becomes involved and results in denudement of the perianal skin. The sex ratio was 58% males to 42% females and the age range was two to 72 years. About 55% were below the age of 20 and 30% below the age of ten years.

Systemic Manifestations

The systemic symptoms are highly variable, depending upon the degree of involvement. Temperature ranges from 101° to 104° F. The attack may last from several days to six weeks, and recurrences or exacerbations have occurred year after year in as many as 25% of the cases.[1] In a review of 31 cases of Stevens-Johnson syndrome,[5] the various clinical manifestations were tabulated (Table 1).

TABLE 1

Clinical Feature	Number of Cases
Rash	30
Stomatitis	27
Conjunctivitis	26
Pharyngitis	18
Cutaneous bullae	17
Pneumonitis	12
Urethritis and/or balanitis and/or vaginitis	10
Anal involvement	3

*From Claxton, R. C.: Med J Aust 1:963, June, 1963.

Mortality

Mortality figures are difficult to obtain. In Claxton's series of 31 cases, there was one death. Earlier studies[4] report mortality figures as high as 10 or 12%. Single case reports in the literature include fatal cases.

Differential Diagnosis

The differential diagnosis may be confusing, especially in the younger patient. Some of the more common disorders to distinguish from Stevens-Johnson syndrome are summarized in Table 2. It should be noted that the laboratory is of no help in specifically diagnosing this syndrome.

Pulmonary

The literature reports involvement of other organ systems in Stevens-Johnson syndrome.[12-14] Of particular interest is the frequency of pulmonary manifestations. In Ashby's and Lazar's analysis of 81 cases, bronchitis or bronchopneumonia occurred in about 30%.[4] The pneumonia is indistinguishable clinically and radiologically from primary atypical pneumonia. A patchy

bronchopneumonia with densities extending out from prominent hilar shadows, often bilateral, is the usual radiographic picture. The term "mucosal respiratory syndrome" was popularized in the Canadian literature because of the frequency of pulmonary involvement. Pneumonia as a manifestation of this syndrome probably represents the greatest single threat to life.[17-18] At autopsy the lungs are heavy and meaty and are studded or completely consolidated with yellowish necrotic zones. There have also been fibrinous exudates covering the lungs. The bronchi described contain thick, creamy, mucoid material thought to be secondary to similar eruptions involving other mucous membranes.

Gastrointestinal

The gastrointestinal tract may be involved in this syndrome. Boe and others[16]

TABLE 2

Guidelines in Differential Diagnosis of Stevens-Johnson Syndrome

Disorder	Distinguishing Characteristics	Laboratory Test
Stevens-Johnson syndrome	Skin lesions are succulent, erythematous papules with "iris" or "bull's-eye" lesions in innermost areas; mucous membranes of the nose, mouth, ears, vagina, rectum, and scrotum may have bullae or vesicles; partial or complete loss of vision may result from ocular lesions.	None
Toxic epidermal necrolysis (Lyell's disease)	Large areas of skin become loose and peel, resembling effect of scalding.	Nikolsky's sign (superficial layer of skin can be rubbed off with light pressure)
Chickenpox	Skin lesions are pruritic and progress in an orderly fashion. Bullous lesions are rare on skin but common in mouth.	None
Vaccinia (following smallpox vaccination)	Lesions progress in stages similar to those of original vaccination; no bullous or polymorphous erythematous lesions appear.	Vaccination 10 to 14 days previously
Diphtheria	Grayish-white thick membrane in throat	Organism isolated
Pemphigus	Protracted course; less polymorphism and configuration	Skin biopsy shows presence of acantholysis
Pemphigoid and bullous dermatitis herpetiformis	More chronic; less mucous membrane and systemic involvement	Skin biopsy shows presence of acantholysis
Bullous contact dermatitis	Location and configuration of lesions suggest external factors; no mucous membrane or systemic symptoms appear; there is a history of allergy.	Patch testing for allergen
Lymphoma	Occasional polymorphous skin lesions appear but clinical picture is sufficient for differentiation.	Biopsy
Septicemia (with blebs)		Identification of infective material
Systemic lupus erythematosus (LE)	There may be typical "butterfly" skin lesion but no erosive vesicular mucous membrane lesions.	Skin punch biopsy; positive LE test; accelerated ESR
Herpetic stomatitis	There are acutely painful lesions on borders of lips and oral mucosa, along with mild constitutional symptoms; the lesions tend to roll with tissue.	Tissue-culture isolation of virus, complement-fixation test

[7]Coursin, D. B.: JAMA 198:134, October 10, 1966.

reported three deaths attributed to gastrointestinal lesions. In two cases the lesions were very much like ulcerative colitis. Other gastrointestinal involvement included necrotizing esophagitis, superficial ulcerations throughout, as well as generalized congested and edematous mucosa. Sigmoidoscopy does not separate the intestinal lesions from ulcerative colitis.

Cardiac

Schartum[13] reported two cases of Stevens-Johnson syndrome with cardiac involvement. One case was that of a 49-year-old man who developed atrial fibrillation and pericarditis with congestive heart failure. The patient recovered completely with the healing of the skin lesions. The other case was also that of transient atrial fibrillation. The author reported that an acute interstitial myocarditis has been noted at autopsy study in a fatal case of Stevens-Johnson syndrome.

Renal

Comaish and Kerr[14] concluded in five cases that an inflammatory renal lesion similar to acute glomerulonephritis is associated with erythema multiforme. This was manifested by albuminuria, microscopic hematuria, cylindruria, and uremia. Hypertension and oliguria were not part of the acute attack. Two of the patients had previous infection by Streptococcus, but not Type 12. The authors pointed out that fatal uremia may develop during the acute illness and recurrent episodes may produce chronic nephritis.

TABLE 3
Attributable Causes of Stevens-Johnson Syndrome

Drugs	Infections	Contactants
Amithizone	Viral	Poison Ivy
Antitoxins	Herpes simplex	
Antidiabetic agents	Coxsackie	
Arsenic	Echo	Internal Malignancies
Barbiturates	Other	
Belladonna	Mycoplasmal	
Bromides	Atypical pneu.	X-ray
Carbamazepine	Bacterial	
Chloroquine	Diphtheria	
Codeine	Erysipeloid	Vaccines
Digitalis	Pneumonia	
Gold salts	Pharyngitis	BCG
Hydantoin	Psittacosis	Polio
Hydralazine	Tuberculosis	Smallpox
Iodides (cough meds)	Tularemia	
Meprobamate	Typhoid fever	
Mercurials	Mycotic	Hormonal
Penicillins	Coccidio	
Phenacetin	Histo	Menses
Phenicarbazide	Protozoan	Pregnancy
Phenolphthalein	Malaria	
Phenylbutazone	Trichomoniasis	
Pyrazolone	Vaginitis	Unknown
Pyrinium		
Quinine		
Salicylates		
Succinimide	Collagen Diseases	
Sulfonamides		
Tetracycline	Food	
Thiouricil	Margarine	
Trimethadione	Chocolate	

Finally, central nervous system involvement with meningoencephalitis has been reported in association with this syndrome.[19]

Histopathology

In erythema multiforme, there is increasing damage to vessels in the dermis. The macule (dilated vessels with subepidermal edema) may increase to papules that develop into "cleavage" vesicles, containing mainly mononuclear cells. Interpretation is that of atypical chronic inflammatory change. Some stress the point that lymphocytes show a tendency towards perivenous localization. Mucosal lesions are similar. Alexander and Cope[2] summarize the histologic abnormalities by (a) epithelial ulceration and (b) widespread necrosis of arterioles and venules with fibrinoid degeneration of associated collagen. They feel that these findings are those of a hypersensitivity reaction. Pearson[20] reported on the ultrastructural alterations at the dermo-epidermal junction in selected blistering diseases. He demonstrated with the electron microscope a striking necrosis of the cytoplasm within the basal cells.

Etiology

The etiology of Stevens-Johnson syndrome remains obscure. Erythema multiforme is a clinically distinct skin reaction of multiple etiologies and is thus considered a syndrome rather than a disease. Coursin[8] points out two main theories: (1) that this syndrome has a single etiology, probably an infectious agent, and (2) that this syndrome represents a symptom complex associated with a large number of conditions, including bacterial infections, viral infections, certain drugs, and a whole host of other miscellaneous conditions.

Bacterial

Many bacterial infections have been cited as attributable causes of this syndrome. These have included diphtheria, various bacterial pneumonias, psittacosis, tuberculosis, tularemia, and typhoid fever. Recurrent streptococcal pharyngitis and tonsillitis have been especially well documented.[14]

Viral

Viral infections are considered causative by many.[12-28] Schmidt[28] isolated herpes simplex virus from an aspirate of a vesicular lesion occurring in this syndrome. Antibodies demonstrated by the herpes virus complement fixation test showed an appropriate rise and fall. Shelley[27] reports a patient who had recurrent erythema multiforme over seven years, each attack being preceded by herpes simplex infection. Herpes simplex has been observed in more than 15% of patients with recurrent erythema multiforme. It was Shelley's feeling that these patients demonstrate a unique hypersensitivity reaction to the herpes simplex antigen. In his patient this was illustrated by repeatedly reproducing vesiculobullous lesions of erythema multiforme type by the intradermal injection of a herpes simplex antigen. The author also points out that herpes simplex may be present in reservoirs such as the vagina and vulvar area, oropharynx, conjunctiva, or penis, and may be activated by various diseases. Other associated viral diseases include measles, mumps, varicella, Coxsackie and Asian influenza.

Of recent interest has been the association of Stevens-Johnson syndrome

with primary atypical pneumonia caused by Mycoplasma pneumoniae.[21-23] Strom [23] reported 16 patients with elevated cold agglutinins and primary atypical pneumonia who developed this syndrome. Four of these patients received drugs prior to the onset of the Stevens-Johnson complex.

Drugs

A host of drugs have been implicated in the etiology.[29-36] Of special interest is the well recognized association with the sulfonamides. Carroll and others,[32] in an FDA survey collected on a worldwide basis, report 116 cases of Stevens-Johnson syndrome associated with long-acting sulfonamide therapy. These were collected over a period from 1957 to 1965. Eighty-one cases occurred in the United States, 27 in adults (33%). Of these 27 patients, five died. The median time of onset of the reaction was about the tenth day following beginning of drug therapy, with a range of two to 24 days. In Claxton's review[5] of 31 cases eight (25%) were attributable to sulphonamides, while in Ashby and Lazar's series of 81 cases, seven (9%) had received sulphonamides previously.[15] Drugs in general were implicated in 42% of Claxton's cases.

Other Factors

Other miscellaneous causes linked to this syndrome have been reported,[37-39] including vaccinations, malignancies, deep x-ray therapy, pregnancy, contactants such as poison ivy, collagen diseases, and foods.

The sudden and widespread mucocutaneous involvement in Stevens-Johnson syndrome caused by such varied factors strongly suggests an allergic or hypersensitivity syndrome. Mackie[40] suggests that initially antibodies are made by the usual immune mechanisms in response to an antigen. A "distorting factor," most likely a drug (quinoneimine breakdown product of sulfonamides), produces distorted antibodies that lose their selectivity for the primary antigen and exert a damaging effect on the normal body.

Treatment

Stevens-Johnson syndrome is considered a self-limiting disease and no specific therapy is available. The course of this syndrome appears to be independent of the type of therapy given. Since this is felt to be a hypersensitivity syndrome, steroids and antihistamines are recommended for the severe cases, but results reported are highly inconsistent. High doses given over a short period are thought to shorten the course of the syndrome. Topical and/or systemic antibiotics are recommended for secondary infection. Symptomatic care for mouth pain, using anesthetic mouth washes as well as proper local therapy for the skin and genitalia, is advised. Local treatment to the eyes becomes extremely important to avoid the serious ocular complications. This includes topical antibiotics and steroids along with warm, moist compresses to avoid the chance of scarring. No attempt should be made to remove any pseudomembranes from the eyes. If drugs are implicated, they should be discontinued.

Summary

Stevens-Johnson syndrome is best defined as an acute inflammatory systemic disease producing a spectrum of clinical patterns. Of primary impor-

tance is the mucocutaneous eruption involving the skin, eyes, nose, mouth, and genitalia. The systemic manifestations are variable, and involvement of the gastrointestinal, pulmonary, cardiac, renal, and central nervous system has been reported. This syndrome is more prevalent in persons under 20 years of age, is somewhat more common in males, and tends to recur in 25% of the cases. Mortality figures range from three to 12%. The etiology remains obscure, but various bacterial and viral infections, and drugs, especially sulfonamides, have been described as causative. The sudden and varied nature of Stevens-Johnson syndrome along with the histopathology strongly support the hypothesis that it is a manifestation of an allergic or hypersensitivity reaction. Although this syndrome is mainly self-limiting, steroids probably shorten its course and are recommended in severe cases.

Case Report

A 22-year-old white male was admitted to Hennepin County General Hospital because of a stomatitis. The patient had noted the onset of a purulent conjunctivitis four days prior to admission. Three days prior to admission a "cold sore" appeared on his lower lip that rapidly progressed to ulcerating lesions over the entire mucosal surface of the mouth. During this time he noted the appearance of erythematous skin lesions on his arm. Two days prior to admission, a clear discharge was seen from the penis. The patient took no drugs and his past medical history was unremarkable.

Physical examination revealed a normotensive young male, temperature 101°, who appeared quite toxic and in distress from pain in his mouth. The patient's conjunctiva were markedly injected bilaterally and there was a serious discharge from the eyes. The corneas were clear. The lips were dry and crusted along with ulcerative lesions. There were ulcerative lesions within the mouth, involving the buccal mucosa extending over the soft palate. Gray-white membranes covered many of these lesions. There were scattered discrete annular erythematous skin lesions over the extensor surfaces of both arms. Some lesions were vesicular with hemorrhagic centers giving the appearance of target lesions. The mucocutaneous junction of the anus was inflamed, and there was a meatal ulcer with clear drainage present on the penis. The rest of the examination was within normal limits.

Initial hemogram, chest film, electrocardiogram, urinalysis, and blood chemistries were normal. VDRL, heterophile, lupus erythematous prep, and cold agglutinin were negative. Throat cultures grew out alpha strep; conjunctival fluid cultures grew out staph; coagulase and urethral cultures were essentially negative. Acute and convalescent sera were negative for herpes simplex.

The patient was placed on parenteral fluids along with penicillin. His mouth pain was relieved with demerol and xylocaine mouth wash. He improved slowly with spontaneous resolution of all his lesions, and he was discharged on the tenth hospital day. There has been no apparent recurrence of signs or symptoms. His discharge diagnosis was uncomplicated Stevens-Johnson syndrome, etiology undetermined.

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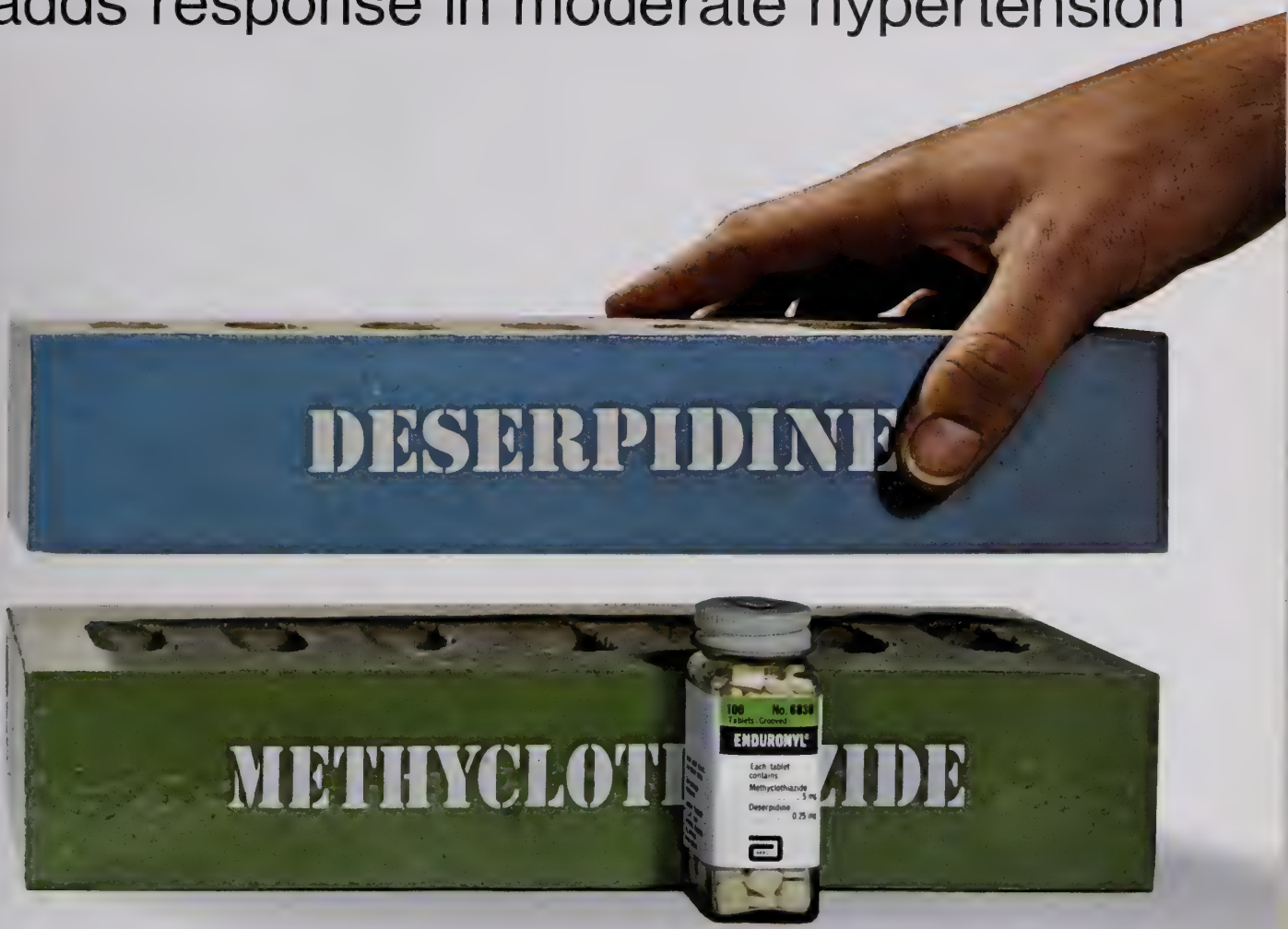
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Less frequent rauwolfia side effects than with reserpine

When you wish to build further response, consider shifting to Enduronyl.

Enduronyl adds a building block of *deserpidine*. This is a purified rauwolfia alkaloid available only from Abbott. It adds good antihypertensive and tranquilizing activity. Yet its incidence of untoward effects, particularly lethargy and depression, is lower than with reserpine.

Enduronyl is available plain or Forte. The latter provides its variation where most helpful, by doubling the deserpidine.

Use Enduronyl for patients throughout the broad range of mild to moderately severe hypertension.

Once a day, every day

ENDURONYL®

METHYCLOTHIAZIDE 5 mg. with DESERPIDINE 0.25 mg. or (FORTE) 0.5 mg.

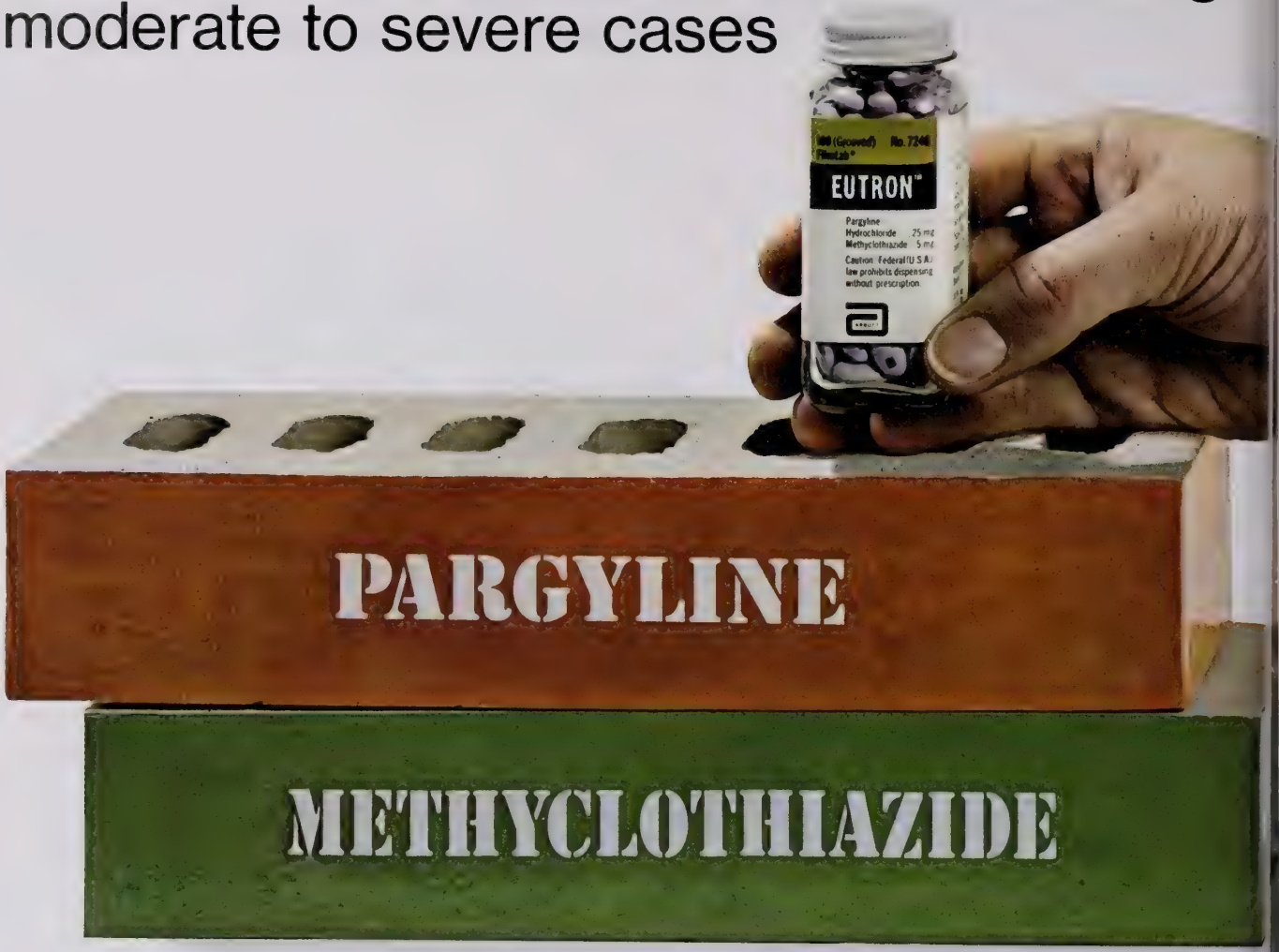
MILD TO MODERATE TO SEVERE



See Brief Summary on final page of advertisement

801094

Eutron: A unique combination for handling moderate to severe cases



Affords almost uniform diastolic reduction in all body positions

Eutron lowers diastolic pressures nearly equally, whether your patient is standing up or lying down.

Thus, in clinical trials, average *standing* diastolic readings were reduced from 112 pre-treatment to 90 post-treatment; *sitting* from 115 to 95; and *recumbent* from 112 to 94.

Note that following Eutron, the diastolic reductions were nearly alike in all three body positions.

Use Eutron for managing your moderate to severe cases. Its building blocks enhance each other; hence lesser doses often suffice.

Once a day, every day

EUTRON™

PARGYLINE HYDROCHLORIDE 25 mg.
with METHYCLOTHIAZIDE 5 mg.

MILD TO MODERATE TO SEVERE



See Brief Summary on final page of advertisement

801094

ENDURON® | ENDURONYL®

METHYCLOTHIAZIDE

Each tablet contains
Methyclothiazide 5 mg. with
Deserpidine 0.25 mg. or 0.5 mg

Indications: Edema and mild to moderate hypertension (Enduron), and mild to moderately severe hypertension (Enduronyl). More potent agents, if added, can be given at reduced dosage.

Contraindications: Sensitivity to thiazides; severe renal disease (except nephrosis) or shutdown; severe hepatic disease or impending hepatic coma (hepatic coma due to hypokalemia has been reported in patients on thiazides). Do not use Enduronyl in severe mental depression, suicidal tendencies, active peptic ulcer, or ulcerative colitis.

Warnings: Consider possible sensitivity where there is history of allergy or asthma. If added potassium is indicated, dietary supplementation is recommended. Reserve enteric-coated potassium tablets for cautious use only when necessary, as they may induce serious or fatal small bowel lesions (stenosis with or without ulceration), cause obstruction, hemorrhage, and perforation often requiring surgery; discontinue them immediately if abdominal pain, distention, nausea, vomiting, or g.i. bleeding occurs. Neither Enduron nor Enduronyl contains added potassium.

Precautions: Use thiazides cautiously in severe renal dysfunction, impaired hepatic function or progressive liver disease; also in pregnancy (bone marrow depression, thrombocytopenia, and altered carbohydrate metabolism have been reported in certain newborn). In surgery, thiazides may reduce response to vasopressors, and increase response to tubocurarine. Antihypertensive response may be enhanced following sympathectomy. Watch for electrolyte imbalance (e.g., hyponatremia) in all patients. In hypokalemia (especially in digitalized patients) give supplemental potassium. In hypochloremic alkalosis, give supplemental chloride.

Use rauwolfias with caution in patients with history of peptic ulcer. Rauwolfias with anesthetics may produce hypotension and bradycardia. Discontinue Enduronyl two weeks before elective surgery. Consider vagal blocking agents during emergency surgery. In epilepsy, adjust anticonvulsant dosage. In electroshock, shorten stimulus strength and duration. In occasional patients with depressive tendencies, rauwolfias may precipitate severe mental depression that usually disappears when drug is stopped.

Adverse Reactions: Thiazide reaction include blood dyscrasias (thrombocytopenia with purpura, agranulocytosis, aplastic anemia); elevation of BUN, serum uric acid or blood sugar; anorexia, nausea, vomiting, diarrhea, headache, dizziness, paresthesia, weakness, skin rash, photosensitivity, jaundice, symtomatic gout, and pancreatitis. Cutaneous vasculitis in the elderly has been reported with other thiazides. Adverse effects with deserpidine are qualitatively similar to those with reserpine, but their incidence is lower. These include nasal stuffiness, abdominal cramps or diarrhea, nausea, headache, weight gain, reduced libido and potency, peptic ulcer aggravation, epistaxis, skin eruption, asthma in susceptible patients, electrolyte imbalance, excessive salivation, and a reversible Parkinson's syndrome. Excessive drowsiness, fatigue, weakness, and nightmares may signal mental depression. Thrombocytopenia, purpura, and a symptom manifested by dull sensorium, deafness, uveitis, glaucoma, and optic atrophy are rare allergic reactions to other rauwolfias. Hypotension from antihypertensive agents may precipitate angina attacks in susceptible individuals. Usually adverse reactions disappear when drug is withdrawn.

EUTRON™

Each tablet contains
Pargyline Hydrochloride 25 mg.
with Methyclothiazide 5 mg.

Indications: For treatment of patients with moderate to severe hypertension, especially those with severe diastolic hypertension. Not recommended for patients with mild or labile hypertension amendable to therapy with sedatives and/or thiazide diuretics alone. It is desirable to establish the dosage of Eutron by administering component drugs separately.

Contraindications: Pheochromocytoma, advanced renal disease, increasing renal dysfunction, paranoid schizophrenia and hyperthyroidism. Hepatic coma has been reported as consequence of hypokalemia with thiazide therapy. Until further experience is gained not recommended for patients with malignant hypertension, children under 12, or pregnant patients.

Concomitant use of the following is contraindicated: other monoamine oxidase inhibitors; parenteral forms of reserpine or guanethidine; sympathomimetic drugs; foods high in tyramine such as cheese; imipramine and amitriptyline, or similar antidepressants; methyldopa. 2 week interval should separate therapy and use of these agents.

Methyclothiazide is contraindicated in patients with known sensitivity to thiazides.

Warnings: Pargyline hydrochloride is a monoamine oxidase inhibitor. Warn patients against eating cheese, and using alcohol, proprietary drugs or other medication without the knowledge of the physician. When indicated, alcohol, narcotics (meperidine should be avoided), antihistamines, barbiturates, chloral hydrate, and other hypnotics, sedatives, tranquilizers, or caffeine, may be used cautiously in reduced dosage. In emergency surgery ¼ to ⅕ the usual dose of narcotics, analgesics, and other premedications should be used avoiding parenteral administration where possible. Carefully adjust dose of anesthetics to response of patient. Withdraw pargyline two weeks before elective surgery.

Warn patients about the possibility of postural hypotension. Those with angina or coronary artery disease should not increase physical activity with an improvement in well being. Pargyline may lower blood sugar.

Avoid use of enteric-coated potassium tablets, as these may induce serious or fatal small-bowel lesions consisting of stenosis with or without ulceration. These small-bowel lesions have caused obstruction, hemorrhage and perforation frequently requiring surgery. Medication should be discontinued immediately if abdominal pain, distension, nausea, vomiting or GI bleeding occurs. These products contain no added potassium salts and if added potassium intake is desired, dietary supplementation is recommended. Coated potassium tablets should be reserved for cautious use when adequate dietary supplementation is impractical. In patients with a history of allergy or asthma the possibility of sensitivity reactions should be considered.

Precautions: Measure blood pressure while patient is standing to determine antihypertensive effect. Use with caution in hyperactive or hyperexcitable persons. Such persons may show increased restlessness and agitation. Withdraw drug during acute febrile illness. Watch patients with impaired renal function for increasing drug effects or elevation of BUN and other evidence of progressive renal failure; withdraw drug if such alterations persist and progress. Use with caution in patients with liver disease. As with all new drugs, complete blood counts, urinalyses, and liver function tests should be performed periodically. With prolonged therapy, examine patients for change in color perception, visual fields and fundi. Also reported have been: blood dyscrasias including thrombocytopenia with purpura, agranulocytosis and aplastic anemia; elevations of BUN, serum uric acid, or blood sugar. Symptomatic gout may be induced. In surgical patients thiazides may reduce response to vasopressors and increase response to tubocurarine.

Adverse Reactions: Pargyline may be associated with orthostatic hypotension. Mild constipation, slight edema, dry mouth, sweating, increased appetite, arthralgia, nausea and vomiting, headache, insomnia, difficulty in micturition, nightmares, impotence, delayed ejaculation, rash, and purpura have been encountered with pargyline. Hyperexcitability, increased neuromuscular activity (muscle twitching) and other extrapyramidal symptoms have been reported in a few patients with reduced cardiac reserve.

During intensive or prolonged therapy, guard against hypochloremic alkalosis and hypokalemia (especially the latter if patient is on digitalis). Observe all patients for signs of hyponatremia ("low salt" syndrome).

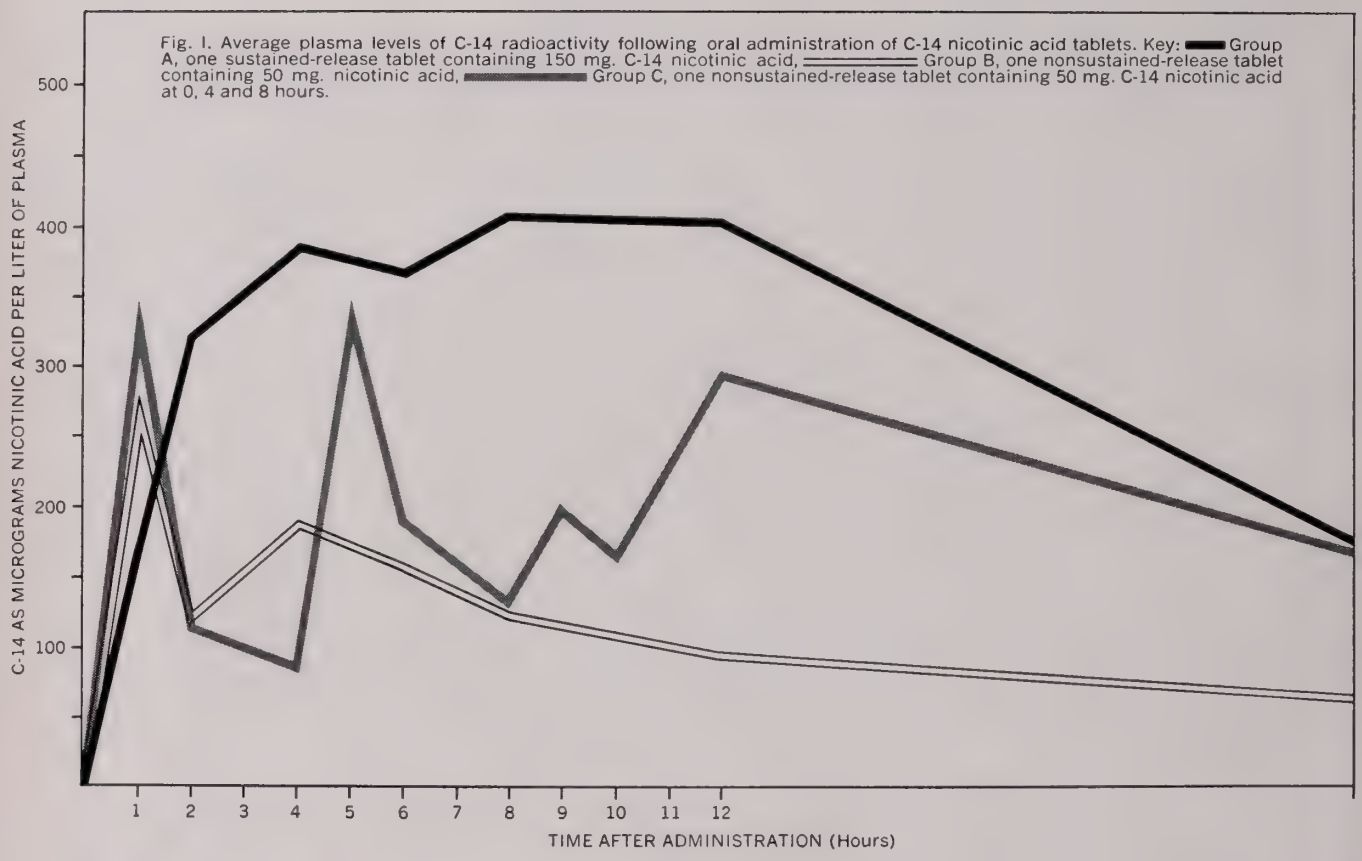
Reported thiazide reactions also include anorexia, nausea, vomiting, diarrhea, headache, dizziness, paresthesia, weakness, skin rash, photosensitivity, jaundice, and pancreatitis. Nocturia has been observed with the combination.

801438

ABBOTT

TM-TRADEMARK

Sustained circulatory, respiratory and cerebral stimulation for the a





(fewer absent doses by absent-minded patients)

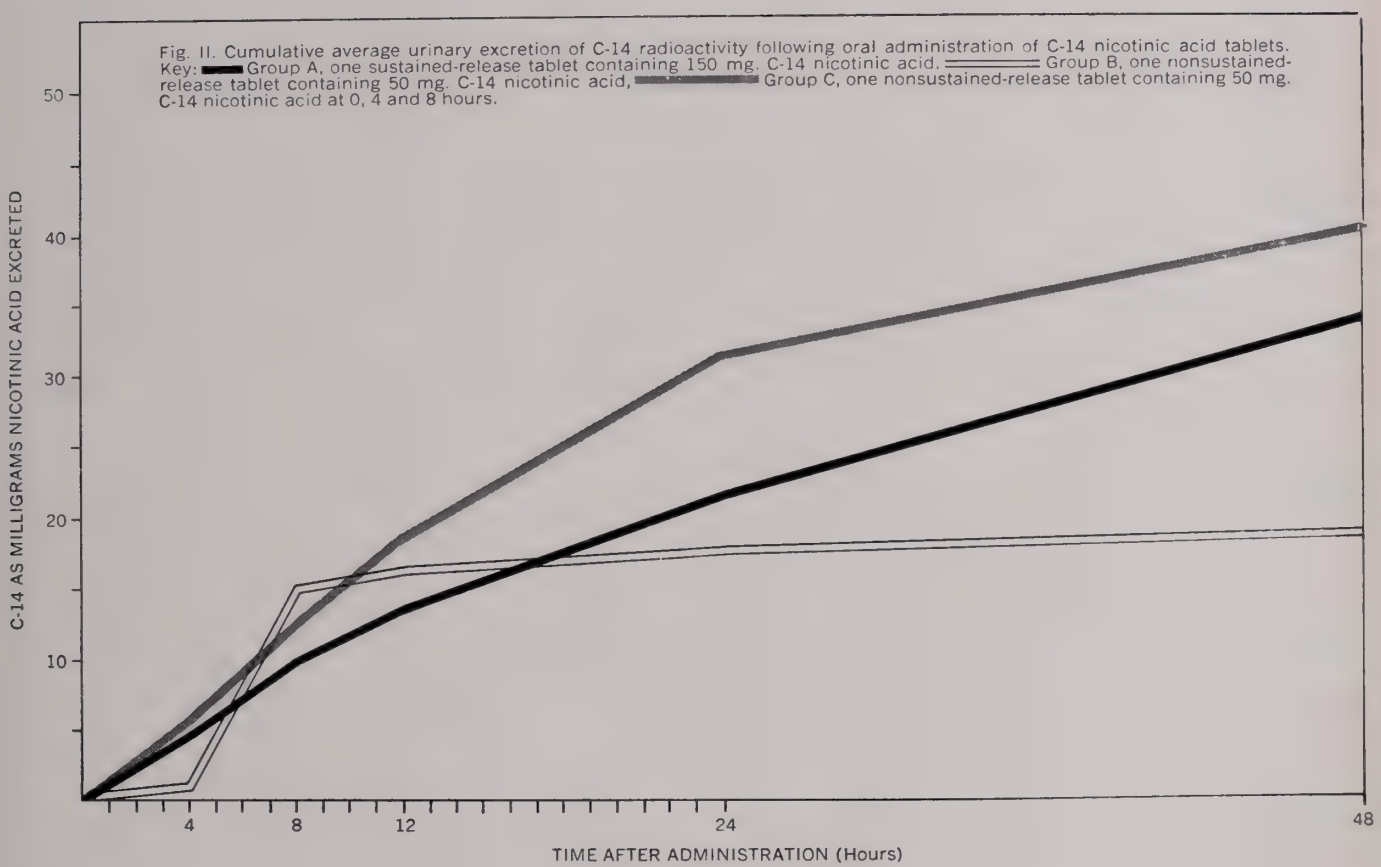
Human volunteer subjects were administered Geroniazol TT tablets with the nicotinic acid component made radioactive with C-14. Plasma and urine samples were analyzed. (See Figures I and II) The radioactive tracer study substantiated the previous clinical evidence that the release of nicotinic acid from the Geroniazol TT tablet produced a gradual rise in plasma levels to a plateau for a total of 12 hours and more.

Such proven sustained activity makes the management of geriatric patients much easier by minimizing the possibility of neglected doses through absent-mindedness or senile confusion. Therapy *can* be continuous on a daily dose of only one Geroniazol TT tablet every 12 hours.

The gradual release of nicotinic acid in Geroniazol TT will provide the well-known peripheral vasodilatation needed in patients with deficient circulation and with a minimum amount (if any) of "flushing." Also, cerebrovascular circulation is complemented by pentylenetetrazol, long-established as a cerebral and respiratory stimulant.

Geroniazol TT improves the typical, unfortunate, signs of senile confusion. Patients become more alert,

aged and debilitated



less confused and moody. Personal care, memory, emotional stability, social attention improve. Fatigue, apathy and irritability are reduced.

A prescription for 100 tablets of Geroniazol TT will permit your patients to enjoy the benefits of time-prolonged nicotinic acid/pentylenetetrazol therapy, at an economical price. Dosage is only one tablet every 12 hours.

Contraindications: There are no known contraindications.

Precautions: Exercise caution when treating patients with a low convulsive threshold.

Side Effects: Side effects are rarely encountered, however due to the vasodilatation effect of nicotinic acid, transitory mild nausea, flushing, tingling and pruritus are possible.

Dosage: One tablet every 12 hours.

Supplied: Prescribe bottles of 100 tablets, to take advantage of recent price reduction.

References: 1. Report by Nuclear Science & Engineering Corp., Pittsburgh, Pa., in files of Philips Roxane Laboratories. 2. Connolly, R.: W. Virginia Med. J. *56*:263 (Aug.) 1960. 3. Curran, T. R., and Phelps, D. K.: Am. Pract. & Digest Treat. *11*:617 (July) 1960.

"First with the Retro-Steroids"
PHILIPS ROXANE LABORATORIES
Division of Philips Roxane, Inc., Columbus, Ohio
A Subsidiary of Philips Electronics and Pharmaceutical Industries Corp.

Geroniazol® TT

nicotinic acid 150 mg., pentylenetetrazol 300 mg.
Tempotrol® Time Controlled Tablet



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Dermatology

Nickel Sensitivity

A 38-year-old woman was seen with an eruption involving both ear lobes (Figure). In addition, she had bilateral circumscribed eczematous lesions on the anterolateral aspects of both thighs. A tentative diagnosis of contact sensitivity to metal was made which was later confirmed by a patch test using a 5% aqueous solution of nickel sulfate. The patient was instructed to avoid earrings and to use protective pads under her garters. With these measures and a topical ointment the eruption promptly cleared.

This relatively simple case serves to illustrate a not too simple problem, that of contact sensitivity to metal. Of the metals producing such sensitivity, nickel is by far the most common. Nickel is usually present alloyed with other metals; some of the more common include alnico, duralium, nichrome, stainless steel and coin alloys. In years past this sensitivity was confined mainly to industrial workers, though today contact allergy to nickel is increasing in the general population and especially among women. Today nickel is found in an ever-increasing number of silver and gold articles with which people may come in



Figure

contact, such as jewelry, buckles, zippers, etc.

Although nickel dermatitis may occur anywhere on the body, certain areas are more common, such as ear lobes, neck, wrists and thighs. Clinically, nickel dermatitis often appears as a chronic eczema with lichenification resembling atopic or neurodermatitis. A characteristic of this dermatitis is its spread to distant areas without apparent direct nickel contact. At present this phenomenon has not been adequately explained.

Of the factors influencing nickel dermatitis, sweating is felt to be of prime importance. Sweat chlorides apparently are necessary in converting the metallic nickel to its soluble salts which in turn produce the sensitivity. In conjunction with sweat, pressure and friction are also important. This may explain the relative frequency of ear-lobe dermatitis secondary to nickel sensitivity in women who wear earrings. Articles containing nickel which are not worn under pressure or are worn on areas where sweating is minimal may cause little or no reaction. A frequently raised question is whether atopic individuals have a greater tendency to develop this type of reaction. To date the evidence does not support this contention. However, there does appear to be increased susceptibility in those individuals with dermatitic and soap-alkali-damaged skin. The mechanism of nickel sensitivity is not clearly defined, although studies tend to support the concept of delayed hypersensitivity in the absence of a hapten* allergic mechanism.

Once this sensitivity develops it tends to remain for many years. Therefore, management of the patient with nickel sensitivity consists of avoidance of direct contact with nickel-containing metals and the use of substitutes such as plastic garter clips. To date, desensitization attempts have been a failure. In addition to avoidance, the use of topical corticosteroid preparations is most helpful in clearing the eruption. Also, the use of a topical corticosteroid prior to the use of a nickel-containing article may be of help in mitigating the reaction.

Willard C. Peterson, Jr., M.D.
Minneapolis, Minnesota

*See Test Your Word Score Page 217.

Minnesota Medicine Cover Photographs

In order to encourage more physicians to submit color slides for use on the cover of MINNESOTA MEDICINE the competition is being discontinued. The picture editor now invites all physician-photographers to send 35 mm. color slides of suitable subjects for consideration as cover pictures. The format must be horizontal because of printing limitations. Pictures high-lighting Minnesota seasons, places, and activities will have an automatic advantage. No limit as to the number of slides sent will be set, but all slides should be individually identified. All slides will be returned. Physicians whose pictures are used as covers will be recognized in MINNESOTA MEDICINE. We can use many more pictures than we have received in the past.

Paradoxical

Two things fill the mind with ever new and increasing wonder—the starry heavens above me, and the moral law within me.—Immanuel Kant



Abstracts, Briefs and Commentaries

HOSPITALIZED MALE PATIENTS' REACTIONS TO A HEART ATTACK

Fifty employed male patients between the ages of 35 and 67 years admitted with a diagnosis of acute myocardial infarction were observed by nurses for emotional response to their illness and interviewed in depth by research psychiatrists. Of the patients 17 had suffered prior heart attacks or had a history of coronary artery disease; 29 were white-collar workers.

Individuals varied in their response to their illness according to their age. Fifty to sixty-year-old patients were more depressed than younger ones; contrariwise, every patient in his thirties was described by the nurses as jovial, unrealistically cheerful or even manic. Finally, patients less than 60 years of age more commonly resisted their treatment than those over 60.

These differences in emotional response appear to relate to general psychological attitudes. For example, there is evidence that young men are highly invested in being active and autonomous and stress their virility with external achievement and denial of weakness. On the other hand, men past 60 are generally more passive, have at least partially resolved their conflicts regarding prestige, and emphasize instead the importance of kindness and morality. Men in their fifties appear to have entered a period of crisis in which there is open conflict over the shift from the active orientation of youth to the passive position of later years. These men still cling to achievement autonomy goal, feeling they must push on, yet doubting their ability to do so. This struggle in the fifties suggests that enforced passivity due to the myocardial infarction may render these individuals susceptible to depressive illness.

Social class influenced the attitudes of the patients toward their illness. The white-collar class, while knowledgeable about their illness, were more skeptical than blue-collar patients regarding the adequacy of care. The white-collar patients were more uncertain and taxed the ingenuity of the medical and nursing personnel in allaying anxiety. The blue-collar workers accepted the authority of the physician and seldom asked the rationale of his treatment; hence these patients did not create difficulty for the staff and were easier to treat. These differences between white- and blue-collar workers became less noticeable in patients who had had two or more myocardial infarc-

tions. In these individuals anxiety increased, as did their skepticism and apprehension about their treatment.

James Janecek, M.D.
St. Paul, Minnesota

Rosen, Jacqueline and Bibring, Grete: Psychological Reactions of Hospitalized Male Patients to a Heart Attack. Psychosomatic Med 28:6:808, 1966.

SEDIMENTATION RATE

The rate at which a patient's red cells sediment often indicates whether that patient has disease. Although Fahraeus described the sedimentation test 46 years ago, precisely why red cells drop faster in the presence of disease remains a mystery. Increased fibrinogen and globulin levels, pregnancy, progestational drugs, anemia, and certain anticoagulants (oxalate and heparin) cause erythrocytes to fall more rapidly. But these factors explain only a few of the cases of increased sedimentation rate.

When red cells sediment faster than 100 mm. in one hour chances are the patient has a potentially fatal disease. Recently two Mayo Clinic physicians studied 263 patients with sedimentation rates of this magnitude, and 152 (58%) had malignancies. All but two tumors had metastasized. Curiously, only 11 patients had multiple myeloma (the one disease we usually associate with high rates), while 36 had lymphoma or leukemias. Only 66 patients (25%) had inflammatory diseases, while 22 had renal disease. In 14 individuals, the cause of abnormality was never determined. Tests which yielded the most diagnostic information included serum electrophoresis, bone marrows, x-rays of abdomen and lumbar spine, and BUNs.

Richard L. Reece, M.D.
Minneapolis, Minnesota

References

1. Fahraeus, R.: The Suspension-Stability of the Blood. Acta Med Scand 55:70, 1921.
2. Zacharski, L. R. and Kyle, R. A.: Significance of Extreme Elevation of Erythrocyte Sedimentation Rate. JAMA 202:264, 1967.

Smallpox on the Frontier

Smallpox remained virulent, but vaccination was beginning to turn back the disease. To some cowpunchers the ounce of prevention seemed much too heavy. Dr. Henry F. Hoyt was vaccinating cowboys at Fort Elliott in the Texas Panhandle. Just as he was finishing up, the superintendent of the LIT Ranch walked into the store where the doctor was wielding the needle. He smoked a cigarette and yawned as he rolled up his sleeve. The doctor inserted the needle; the rancher looked at the tiny drop of blood oozing from his brawny arm and fell to the floor in a faint. The cowboys present allowed that such a "perfect shot" entitled the doctor to carve a notch on his gun.

Up in Montana, Dr. John Lewis Weitman of Great Falls was noted for his effective treatment of smallpox. His patients even recovered without scars. His explanation: "I get them so damned drunk they can't raise their arms to scratch the first three days."*

*Richard Dunlop, M.D.: Doctors of the American Frontier.

Qualifications

A doctor's character should be square, his knowledge round, his gall bladder large and his heart small.—Chinese proverb

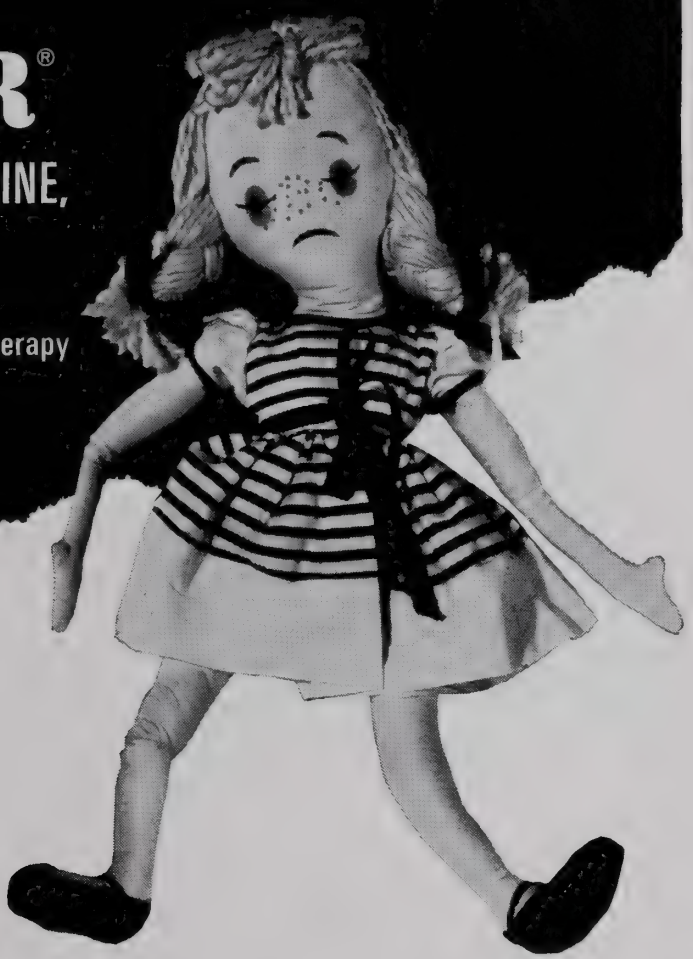
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Letter® provides all the advantages of the synthetically pure chemical sodium levothyroxine. Dosage is precise and potency is consistently uniform.

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Letter® is micronized to provide maximum opportunity for full absorption and clinical response.

In addition Letter® is distinctively color coded with an identifying number stamped on each tablet to provide accurate dosage control.

Indications: Hypothyroid conditions. **Contraindications:** Thyrotoxicosis, acute myocardial infarctions unless associated with hypothyroidism. In hypothyroidism with hypoadrenalism coadministration of corticoids with LETTER® is recommended. **Precautions and Side Effects:** Excessive dosage may result in diarrhea, cramps, palpitation, nervousness, rapid pulse, sweating. If symptoms appear, discontinue medication for several days, then reinstitute at a lower level. Since myxedema patients with heart disease may suffer seriously from abrupt increases in dosage, caution should be exercised in adjusting dosage. **Dosage:** Generally, the initial adult dosage is 0.1 mg. daily. This may be increased in small increments every one to three weeks until proper metabolic balance is achieved. **Available:** Bottles of 100 tablets, in six potencies: 0.025 mg. (violet), 0.05 mg. (peach), 0.1 mg. (pink), 0.2 mg. (green), 0.3 mg. (yellow), and 0.5 mg. (white).

ARMOUR PHARMACEUTICAL COMPANY • CHICAGO, ILLINOIS



Phenaphen® with Codeine

the only leading compound analgesic that calms instead of caffeinates

Each capsule contains:

Phenobarbital (¼ gr.)	16.2 mg.
(Warning: may be habit forming)	
Aspirin (2½ gr.)	162.0 mg.
Phenacetin (3 gr.)	194.0 mg.
Hyoscyamine sulfate	0.031 mg.
Codeine phosphate	¼ gr. (No. 2), ½ gr. (No. 3), 1 gr. (No. 4)
(Warning: may be habit forming)	

Contraindications: Hypersensitivity to any ingredient.

Precautions: As with all phenacetin-containing products, avoid excessive or prolonged use.

Side Effects: Side effects are uncommon—nausea, constipation, and drowsiness have been reported.

A-H-ROBINS

A. H. ROBINS CO., INC., Richmond, Va. 23220

For your impatient cold patients

Two sprays from NTZ Nasal Spray—and nasal congestion, rhinorrhea, sneezing are reduced for *immediate* comfort for patients with colds.

NTZ is more than a simple vasoconstrictor. It contains:

Neo-Synephrine® **(brand of phenylephrine) HCl 0.5 per cent,** the major component, virtually synonymous with fast, efficient but gentle nasal vasoconstriction on contact.

Thenfadil® **(brand of thenyldiamine) HCl 0.1 per cent,** topical antihistamine for reduction of rhinorrhea, sneezing or itching. It combats the allergic reactions that may occur in colds or sinusitis.

Zephiran® **(brand of benzalkonium, as chloride, refined) 1:5000,** antiseptic preservative and wetting agent to promote penetration and spread of the formula.

NTZ is well tolerated. Used in a cold it may help prevent sinusitis by opening sinus ostia and permitting drainage. It may also be used in sinusitis to help establish drainage.

The spray is best used twice, the second a few minutes after the first, repeated every three or four hours as needed. NTZ is for temporary relief of nasal symptoms, and overdosage should be avoided.

Supplied: NTZ Nasal Spray, plastic squeeze bottles of 20 ml.; NTZ Nasal Solution, bottles of 30 ml. (1 fl. oz.) with dropper.

Winthrop

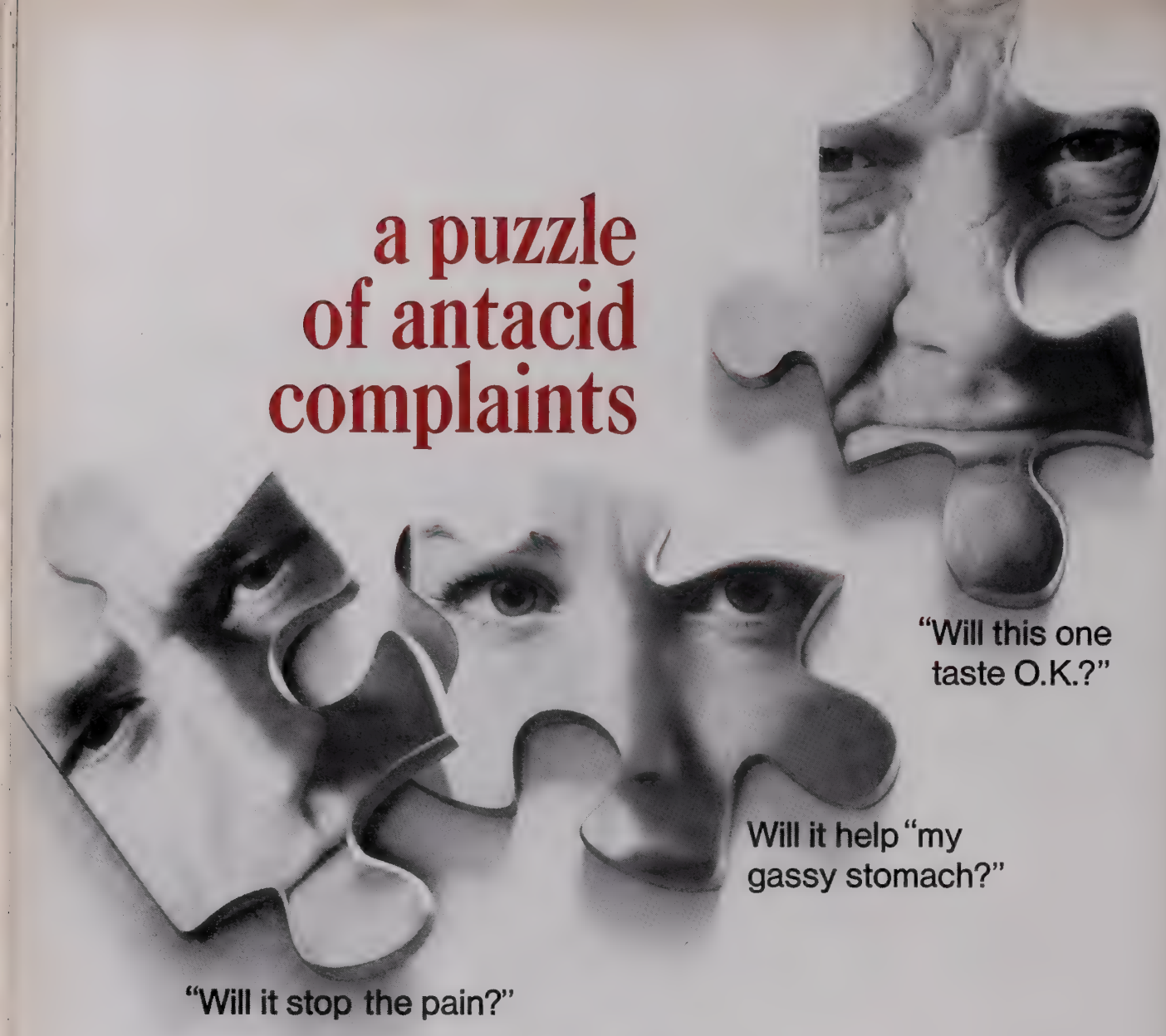
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NTZ®
NASAL SPRAY

relieves
nasal symptoms
on contact

a puzzle of antacid complaints



Mylanta®

aluminum and magnesium hydroxide *plus* simethicone

a solution to peptic ulcer distress

Effective neutralization—
with the two most widely prescribed antacids: aluminum and magnesium hydroxides.

Concomitant relief of G.I. gas distress—
with the proven[1] defoaming action of simethicone.

Prolonged acceptance confirmed—
in 87.5% of 104 patients after a total of 20,459 documented days of therapy.[2]

Composition: Each Mylanta chewable tablet or teaspoonful (5 ml.) contains: magnesium hydroxide, 200 mg.; aluminum hydroxide, dried gel, 200 mg.; simethicone, 20 mg.
Dosage: One or two tablets (well chewed or allowed to dissolve in the mouth) or one or two teaspoonfuls to be taken between meals and at bedtime.

References: 1. Hoon, J.R.: Arch. Surg. *93*:467 (Sept.) 1966.
2. Danhof, I.E., Personal communication.

Stuart
Division/Pasadena, Calif.
ATLAS CHEMICAL INDUSTRIES, INC.



Book Reviews

Books are lighthouses erected in the great sea of time.—E. P. Whipple

DIABETES MELLITUS: DIAGNOSIS AND TREATMENT. Volume 2. Editors: George J. Hamwi, M.D. and T. S. Danowski, M.D. Prepared under the auspices of the Committee on Professional Education of the American Diabetes Association, Inc. New York, N. Y., 1967.

This 240-page book addresses itself to the practicing physician in clear and concise language. The organization of the material is excellent. Research data are used whenever they may have a bearing on the clinical management of the diabetic patient. The book is easily read and understood.

The classification of secondary diabetes is clear, brief and lucid, but it should include pheochromocytoma along with hyperpituitarism, Cushing's syndrome, and the hyperthyroid states. The emphasis on the influence of exercise in the treatment of diabetes is excellent. One would wish that the Somogyi-effect as a consequence of imprudent insulin therapy had received more emphasis.

The discussion of the treatment of diabetic acidosis and coma might have gained more practical usefulness if it had been demonstrated by means of a detailed sample protocol. Finally, the insulin dosage recommended for the treatment of diabetic acidosis and coma is high enough to result in life-threatening hypoglycemia within the first 24-36 hours of therapy.

With the exception of the just cited items the book is a valuable guide for the day-to-day treatment of the diabetic patient, as well as for the management of emergencies.

H. H. Zinneman, M.D.
Minneapolis, Minnesota

GREAT IDEAS IN THE HISTORY OF SURGERY—Leo M. Zimmerman and Ilza Veith. 547 Pages. Dover Publications, Inc., New York. 2nd Revised Edition.

This book is a large compendium emphasizing the ideas which have generated progress in the science and art of surgery rather than dealing with the details of biography. The biographical development is, of course, not eliminated but takes its proper place in the development of background for the ideas developed by the great men in surgery.

The reader will undoubtedly be intrigued by the originality of numerous relatively unknown contributors to the advancement of medicine. The "great" men of surgery are properly developed, and it is very gratifying reading to realize the multitude of ideas which have made these men great.

If a reader indulged in no more effort than skip reading, he would discover the very ancient origin of many significant contributions which originate the practices of today. A more careful reading will demonstrate the rebirth of many great ideas that have been forgotten or have fallen into disuse for prolonged intervals.

One could recommend this as a baseline or background reading to the Journal of the History of Medicine.

This is a highly commendable work which deserves to be on the shelf of every surgeon, whether he desires to study it intensively or use it for entertainment as occasional pickup reading.

J. H. Strickler, M.D.
Minneapolis, Minnesota

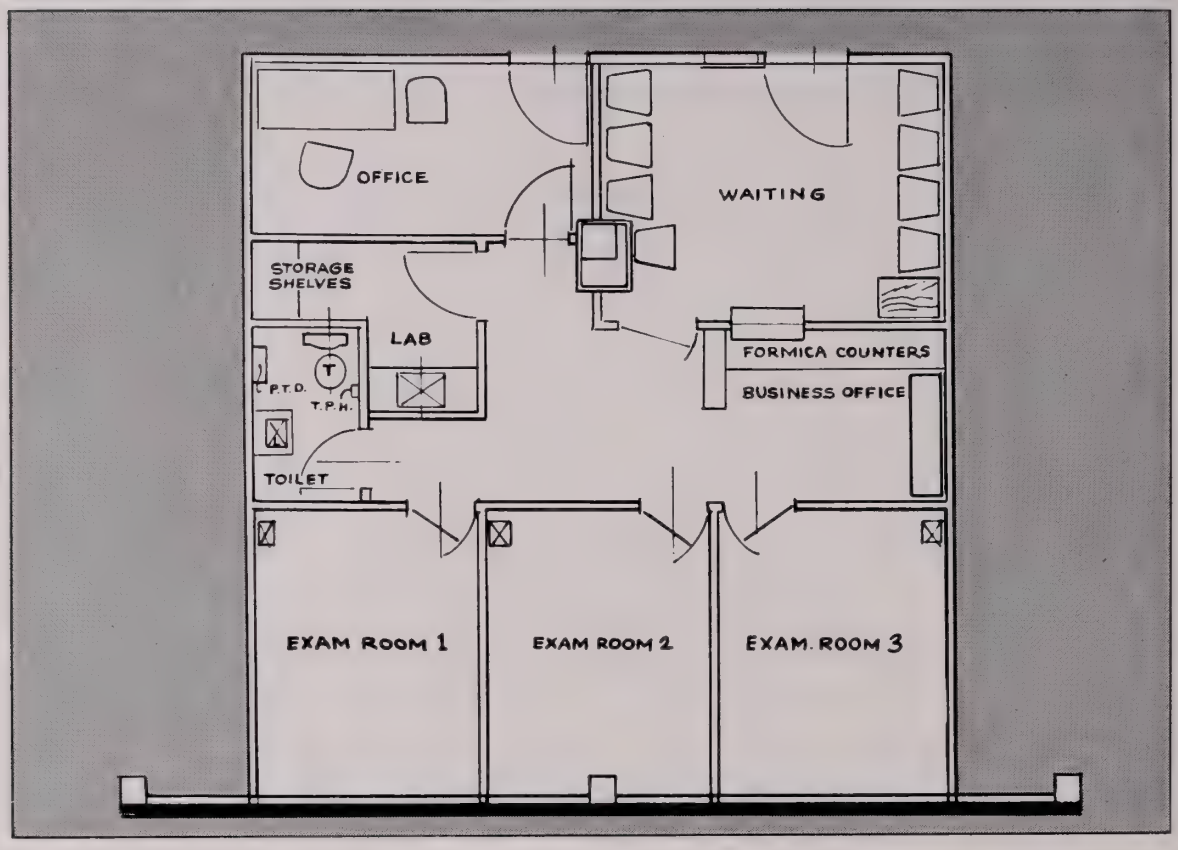
PULMONARY INSUFFICIENCY AND RESPIRATORY FAILURE—Giles F. Filley, M.D. Cost: $7.00. Lea & Febiger, Washington Square, Philadelphia, Pa.

This 162-page monograph provides the physician with an excellent, concise review of essential clinical pulmonary physiology and the symptoms related to a disturbance of the normal ventilatory and diffusion function. Nicely presented is the explanation of the disturbed ventilatory-pulmonary blood flow ratio, hypoxemia, shallow breathing and lung compliance.

In addition, the practical aspects of the recognition of pulmonary insufficiency, the treatment thereof, and the concept of a "respiratory care unit" merit wide application in every hospital and by every physician. The bibliography is extensive and pertinent if further reading is desired. The illustrations (28) are well done and easily interpreted.

This book is thoroughly enjoyable reading. Certain books are the type to keep close at hand for those precious 15-20 minutes of relaxation and learning, at the office, home, or hospital. Dr. Filley and Staff have assembled a monograph to be read and reread—a real pleasure to review.

J. T. Grismer, M.D.
Minneapolis, Minnesota



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- Put your name in lighted Plaza directory exposed to more than 500,000 persons every month.

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Precautions—Overgrowth of nonsusceptible organisms may occure. Constant observation is essential. If new infections appear, appropriate measures should be taken. In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment.

Side Effects—Gastrointestinal system—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin—maculopapular and erythematous rashes. A rare case of exfoliative dermatitis has been reported. Photosensitivity; onycholysis and discoloration of the nails (rare). Kidney—rise in BUN, apparently dose related. Transient increase in urinary output, sometimes accompanied by thirst (rare). Hypersensitivity reactions—urticaria, angioneurotic edema, anaphylaxis. Teeth— dental staining (yellow-brown) in children of mothers given this drug during the latter half of pregnancy, and in children given the drug during the neonatal period, infancy and early childhood. Enamel hypoplasia has been seen in a few children. If adverse reaction or idiosyncrasy occurs discontinue medication and institute appropriate therapy.

Average Adult Daily Dosage: 150 mg q.i.d. or 300 mg b.i.d. Should be given 1 hour before or 2 hours after meals, since absorption is impaired by the concomitant administration of high calcium content drugs, foods and some dairy products. Treatment of streptococcal infections should continue for 10 days, even though symptoms have subsided.

In the treatment of syphilis a dosage schedule of a total of 12 to 18 Gm. given in equally divided doses over a period of 10 to 15 days should be followed. Close follow-up observation of the patient is recommended, including appropriate laboratory tests, since demethylchlortetracycline has not had adequate evaluation in all stages of syphilis. Spinal fluid examination should be included as part of this follow-up.

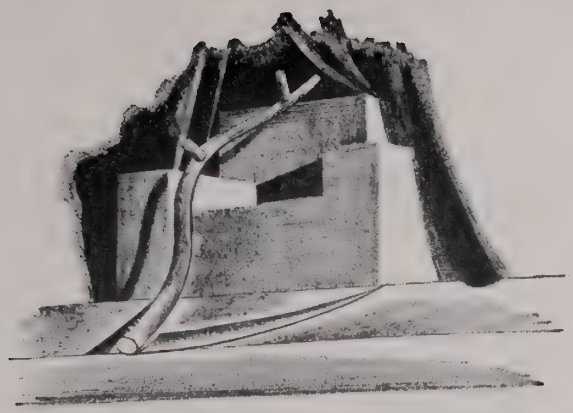
Acute gonococcal anterior urethritis in males has been treated effectively with a single dose of 600-900 mg. of DECLOMYCIN Demethylchlortetracycline. Individuals unable to tolerate large single doses due to gastrointestinal side effects may be treated with 150 mg. every 6 hours for a minimum of 4 doses or 300 mg. every 12 hours for a minimum of 2 doses. Females should be treated with a dosage of 150 mg. every 6 hours or 300 mg. every 12 hours until a cure is effected.

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In Memoriam

Gone before to that unknown and silent shore.—Lamb

CARL O. KOHLBRY, M.D.

Dr. Carl O. Kohlbry, 70, Duluth physician and health director of the Board of Education, died November 29. Born in St. Louis, Missouri, he was a graduate of Washington University Medical School. He came to Duluth in 1921 and was engaged in private practice until 1954 when he became health director of the board of Education.

He was a member of the St. Louis County Medical Society and the American Medical Association and a Life Member of the Minnesota State Medical Association.

He is survived by his wife, two sons and a daughter.

ALFRED L. VADHEIM, M.D.

Dr. Alfred L. Vadheim, who practiced medicine in Tyler, Minnesota, for more than fifty years, died November 26, at the age of 83. He was born in Garretson, South Dakota, graduated from the University of Minnesota in 1909, and went to Tyler the following year. Early in his career, he organized and equipped Tyler's first 5-room hospital.

Dr. Vadheim was a member of the American College of Surgeons, the Lyon-Lincoln County Medical Society and the American Medical Association and a Life and 50 Club Member of the Minnesota State Medical Association.

He is survived by his wife, two daughters, and three sons, Dr. James Vadheim of Tacoma, Washington, Dr. Lewis Vadheim of Pomona, California, and Dr. Robert Vadheim of New York City.

JOHN L. SHELLMAN, M.D.

Dr. John L. Shellman, formerly of St. Paul, died on November 23 in Palisades, California. He was 91. Born in Fergus Falls, he graduated from the University of Minnesota Medical School in 1903. He practiced on the Mesaba Range at Nashwauk and for more than twenty-five years in St. Paul.

He was a member of the American Medical Association, American College of Surgeons, American Academy of Ophthalmology and Otolaryngology, Minnesota Society for the Prevention of Blindness and the Ramsey County Medical Society. He was a 50 Club and Associate Member of the Minnesota State Medical Association.

He is survived by his wife and daughter. Dr. Joseph F. Shellman of St. Paul is his brother.

RAYMOND M. EPPARD, M.D.

Dr. Raymond M. Eppard, 73, Cloquet surgeon, died January 1. He was born in Racine, Minnesota, and received his medical degree from the University of Minnesota.

He was a member of the American Medical Association, the Minnesota State Medical Association and the St. Louis County Medical Society.

He is survived by his wife, two daughters and a son.

CHARLES BISHOP WILL, M.D.

Dr. Charles B. Will, 56, International Falls physician, died December 27, while shoveling snow in the driveway at his home. Born in Bertha, Dr. Will practiced in International Falls since 1955. He was a graduate of the University of Minnesota Medical School.

Dr. Will was past president of the Upper Mississippi Medical Society; past president of the Range Medical Society; a council member of the Minnesota Academy of General Practitioners; medical representative of the Falls Memorial Hospital Board, and a member of the American Medical Association and the Minnesota State Medical Association.

He is survived by his wife and a daughter.

LEROY J. HOLMBERG, M.D.

Dr. LeRoy John Holmberg, 92, died December 7 in Canby. Born in LaCrosse, Wisconsin, Dr. Holmberg graduated from the University of Illinois Medical School. He practiced medicine in Cashton, Wisconsin until 1908 when he moved to Canby where he practiced for fifty-five years, retiring in 1963.

He served as a medical officer during World War I; a past president and secretary-treasurer of Camp Release District Medical Society; served as surgeon for the Chicago and North Western Railroad, was a member of the American Medical Association and a Life and 50 Club Member of the Minnesota State Medical Association. He is survived by his son.

OLIVER M. PORTER, M.D.

Dr. Oliver M. Porter, 90, Atwater physician, died September 7. He received his medical degree from the University of Minnesota and was licensed in 1905 to practice medicine.

Dr. Porter was a member of the American Medical Association and the Kandiyohi-Swift-Meeker County Medical Society and an Associate and 50 Club Member of the Minnesota State Medical Association.



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Contraindications: Edema; danger of cardiac decompensation; history or symptoms of peptic ulcer; renal, hepatic or cardiac damage; history of drug allergy; history of blood dyscrasia. The drug should not be given when the patient is senile or when other potent drugs are given concurrently.
Warning: Tandearil is an analog of phenylbutazone; sensitive patients may be cross-reactive. If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Instances of severe bleeding have occurred. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy. Use with great caution in the first trimester of pregnancy.
Precautions: Before prescribing, carefully select patients, avoiding those responsive to routine measures as well as contraindicated patients. Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patient should not exceed recommended dosage, should be closely supervised and should be warned to discontinue the drug and report immediately if fever, sore throat, or mouth lesions (symptoms of blood dyscrasia); sudden weight gain (water retention); skin reactions; black or tarry stools or other evidence of intestinal hemorrhage occur. Make regular blood counts. Discontinue the drug immediately and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.
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holding dietary salt, reduction in dosage or use of diuretics. In elderly patients and in those with hypertension the drug should be discontinued with the appearance of edema. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. The patient should be instructed to take doses immediately after meals or with milk to minimize gastric upset. Mild drug rashes frequently subside with reduction of dosage. However, rash accompanied by fever or other systemic reactions usually requires withholding medication. Purpuric rash has also been reported. Agranulocytosis or a generalized allergic reaction similar to a serum sickness syndrome may occur and require permanent withdrawal of medication. Stomatitis, salivary gland enlargement, vomiting, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported. While not definitely attributable to the drug, a causal relationship cannot be excluded. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.

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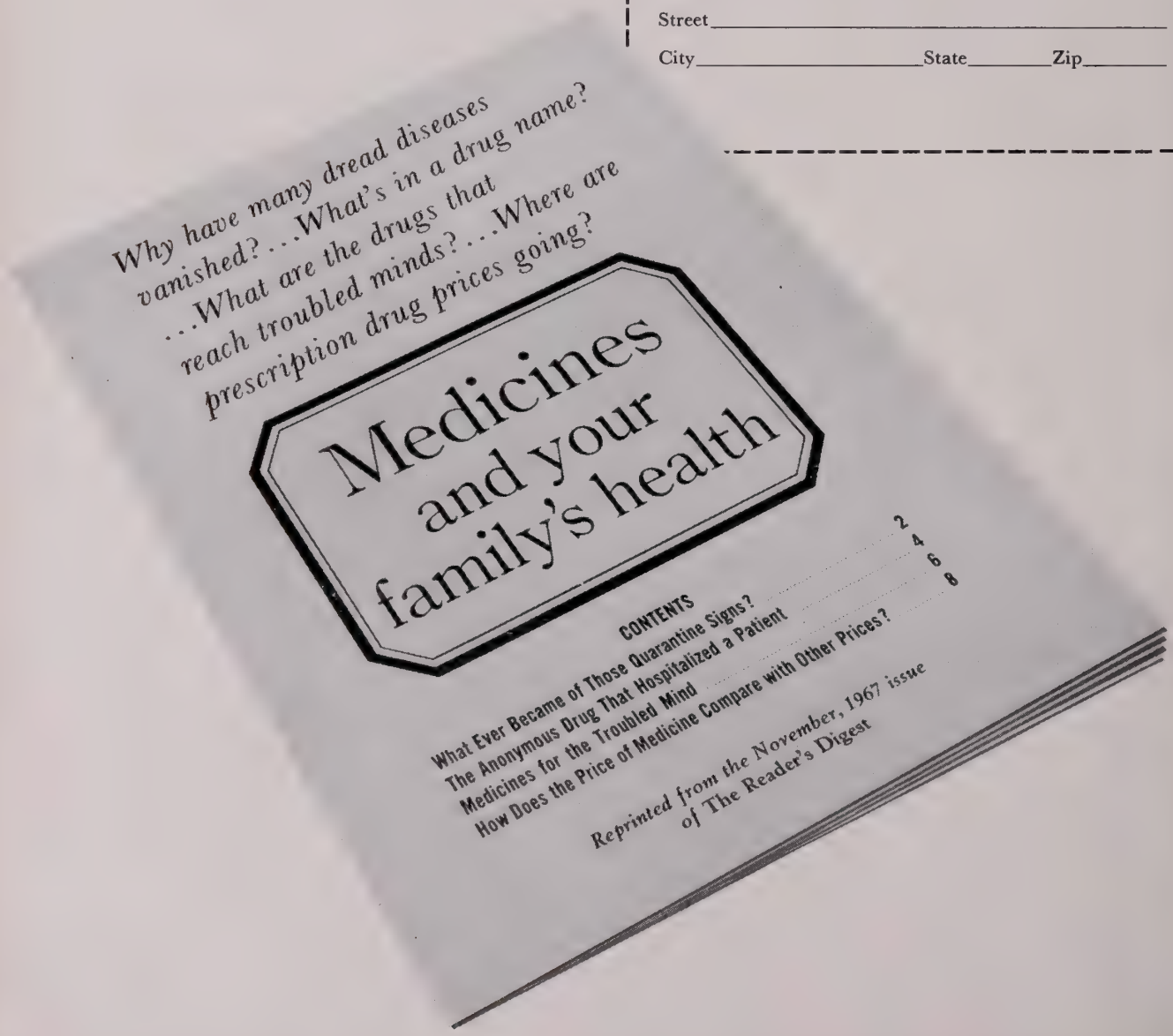
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Special Article

Paranoid Wife Syndrome

DONALD C. CARTER, M.D.*
Columbia, Missouri

A PATIENT with this syndrome complains of low energy and has an overlay of neurotic depression. She initially perceives her problem as a medical one, but when careful examination shows no organic disorder, she exhibits more neurotic complaints associated with the persistent view that her husband is somehow to blame.

In our series of 32 intensively treated cases, she has usually been married five to ten years, and may have as many children. Her low psychic energy manifests itself by a syndrome of clinging dependency, a self-critical, depressed mood, and the conviction that the dependency claims and demands of husband and children are inundating. She believes that if she were loved more sincerely and given more time or indulgent attention a rise in energy would occur. Seldom are objective reasons for the low energy recognized by the patient herself. The psychic delusion of a socially deprived and exploited life quickly becomes the topic of conversation with such a patient.

The experienced practitioner knows that variations in women's energy are frequent and difficult to explain. His initial approach is usually conservative and supportive; and he anticipates a natural resolution. The case becomes an office problem only when usual measures do not help and a tranquilizer or energizer prescription is rejected as merely temporary in effect. He may then decide to spend more time listening to the patient in order to get to the bottom of the problem. With faith in the rationality of the human mind, he awaits his chance to formulate what is wrong and offer corrective counsel. In the more severe forms of this disorder his efforts are doomed to failure, not because he is a poor counsellor or is unsympathetic, but because the natural course of the disorder is a progressive one. It begins with energy depletion revolving around feminine duties of home-making and child-rearing and proceeds to the gradual precipitation of blame-shifting paranoid delusions,

*Assistant Professor of Psychiatry, University of Missouri.

centering around the basic idea that the husband is at fault. This clarification may take several months of follow-up visits, during which the patient may vary the degree of the blaming process or even abandon it spontaneously for many months for no obvious reason.

Medical History:

The general medical history of these female patients often contains several recent humiliating features. Dexedrine addiction may have carried them for a while, but now abuse or intolerance makes discontinuing it mandatory. Secondly, an unfortunate obstetrical experience may have resulted in a feeling of failure. Thirdly, a child may have been seriously ill, the mother perceiving the need for medical care only dimly at first, later with greater clarity but much self reproach. Problems in obstetrical and pediatric care associated with difficult labor are common examples of humiliation to a woman's self esteem, but are not generally recognized as such.

The Husband:

As treatment progresses, the physician feels it important to get the allegedly "depriving" and "persecutory" husband in for a conference and confrontation. This interview has many predictable features and a characteristic course. The husband is usually a remarkably passive fellow who finds numerous excuses not to come in. When he finally does he listens quietly, giving the impression of imperturbability as his chief character trait. But good rapport and direct confrontation will eventually bring a response: he notes that he could be a better husband if only she were a better wife.

The Wife:

He then recites a litany of wifely duty derelictions on her part: for example, that she is tired and irritable much of the time; that housework is neglected; that children are poorly cared for; that meals are irregular, and that sexual intercourse is refused him more often than not. When the physician says that she performs poorly due to low psychic and somatic energy he finds this explanation falling on deaf ears.

A serious and empathic search from the husband's point of view elicits disbelief that womanly performance has anything to do with her state of mind. He believes that his wife should perform well if only told to do so. He presents the idea in a moral-intellectual manner, ignoring her emotional needs as unworthy of consideration, an attitude strongly psychotogenic for her already weakened state. For him to quote religious and other patriarchal authorities to support his point of view is also futile.

Follow-up:

Additional interviews may get him to soften this rejecting and demanding attitude and concede that she may have a point. He may then reveal that she blows up into psychotic rages when he does certain things he likes and she hates; but there are also rages for which he cannot recognize a provocation. The situations which provoke her are self-indulgent pleasures which he is reluctant to admit or renounce. Trial runs of giving them up, however, may help her, if she can immediately respond with more enthusiastic energy and housework output. This bears out the idea that he will get further by cooperation than by vindictiveness.

Depending on the length and severity of the psychotic trends operating in her personality, healing results may be apparent at this point. The remainder of this paper speaks to the more severe cases where erratic performances continue to disrupt and destroy the family's biosocial functions. Then the husband returns to say that she remains hostile and critical, rejecting his best efforts, and that nothing he does helps.

Marriage Counseling:

At this point the physician may despair and refer the case to a marriage counselor or to the Community Mental Health Center. Even when these consultant resources are available and the family cooperates, the family physician continues to have much responsibility. Chemotherapy and advice about the possibility of suicide or the feasibility of divorce are examples of his responsibility.

Indications for Poor Prognosis:

Severe ambivalence in the patient's feelings toward the husband may paralyze her using any advice or coming to any decision on how

to help herself. This commonly-found mental symptom is the worst one in the long run and responds at best only partially to treatment.

A complete inability and refusal by the husband to give up the self indulgences which interfere with his function as a father at home is commonly exemplified in our series by long hours of unnecessary over-work, which he claims gives his life the energy and meaning which his wife has failed to provide. Therefore her needs come second. He also fails to recognize his obvious flight from her hostility. When he is pressed to correct this point, he again argues on the irrationality of her needs.

Sexual impotency reaction in the husband to the wife's high level of hostility bodes a bad outcome.

Perception by her that the impotency is punitive and, further, that it proves her not to be a desirable woman again worsens the relationship.

Sadistic and masochistic fights with beatings may occur, the descriptions of which often defy our imaginative credulity.

The gradual psychotic reorganization of the conflict within the wife's personality, in which she develops a psychologically aversive reaction to all the husband's gratifications, only completes the alienation which has often been operative from the first in more hidden or partial forms.

Another somewhat different tactic is a motherly, indulgent attitude toward the patient by the spouse, also often interpreted to mean that she is a failure as a mother and homemaker. This reaction on her part is often a further alienating one for her women friends who may have been supportive up to this point. They see the husband's behavior only for its conscious intent, whereas she registers a deeper, more subtle message.

In general, anything which makes her feel less feminine is a potentially worsening factor.

Indications for a Good Prognosis:

Generally helpful is any set of experiences or limiting circumstances which curtails those facets of the husband's behavior perceived by the wife as an affront.

A direct restructuring of the marital relationship so as to change the malignant combination of the wife's great expectations and the husband's cool passive denial of their existence would be an ideal goal. If marital counseling can resolve this impasse, then her symptoms diminish.

Her employment outside the home, where working relationships are inspiring and her opinions influential, is generally helpful.

Often a change for the better results when the husband disavows the attitude that womanly performance is simply obedience to the wise directives of a man. This attitude applies to masculine performance and should not be mistakenly transferred to the feminine sphere.

Outcome:

Suicide is a definite possibility when psychologically paralyzing ambivalence is severe and the woman's anger internalized. Additional motives for this drastic step are two-fold: the patient may be so well structured in her either-or thinking that she simply cannot see any relief other than oblivion; or she may want to prove to the world that her husband was so impossibly selfish that this stark alternative was preferable. When serious suicide attempts are repeated, vigorous intervention by family, pastor, or attorney is necessary. An ambivalent component of the patient's personality will, of course, resist any maneuver by others.

Divorce for Social Reasons:

Divorce is often an answer that the patient herself arrives at when she finds solid support outside the illusory props of her miserable status quo. I have seen welfare agencies and other counselors recommend divorce, usually based on the extent of social indecency involved. But this is an example of a social reason, not a psychiatric one.

Divorce for Psychiatric Reasons:

Diminution of the rage symptom by the physical absence of the spouse should be well demonstrated. A trial absence of at least 90 days will differentiate the wife capable of sustained logic. Many an inadequate wife will ambivalently switch from hate to loneliness on about the 45th day and then begin to deny the existence of the previous problems. Experi-

ence in dealing with loneliness is necessary for her to avoid humiliating repetitions and further damage to her self-esteem.

When she appears able to rechannel the energy of her rages into constructive outlets of work and family guidance, she then has a greater opportunity for self-fulfillment.

When she appears able to accept the idea of self-support, which is sure to become necessary eventually, divorce is a way of ending the degrading and hostile dependency and therefore a good thing for her.

When she appears able to relate to another man in a genuinely complementary way, showing little or no aversive reaction to whatever his narcissistic character traits may be, the possibility of a successful second marriage is good.

When supportive relatives are available or when the local welfare or other agency can be supportive without being rebuffed by the hostility in her dependency, then she should choose this escape.

The physician's role may not necessarily be the working out of these alternatives, but he should be able to clarify them for other interested parties. He should guide the patient to adequate emotional support from others, help provide this himself, and work to protect her from any further humiliation to her womanly self-esteem. And last, but not least, he should evaluate and revise these criteria. Careful documentation of his successful cases can be very reassuring for managing future cases.

He may see his role as chemotherapeutic alone, which may be sufficient in some cases. Phenothiazines and antidepressants may control the rages and the physiologic equivalents, allowing the patient to evade the paranoid stage and, in a crippled and unresolved way, live with her problem. Supportive psychotherapy often can do the same thing, thereby postponing the day of reckoning until a more favorable time.

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Medical Men on Postage Stamps

William J. Mayo (1861-1939) and his brother, *Charles H. Mayo* (1865-1939), surgeons who founded the Mayo Foundation for Medical Education and Research in affiliation with the University of Minnesota at Rochester, Minnesota, appear on a United States postage stamp issued in 1964. Their heads as shown on the stamp are from a sculpture by James Earle Fraser.

Leopold Auenbrugger (1722-1809) was a Viennese physician, medical writer, and discoverer of chest percussion as a diagnostic procedure, the principle of which occurred to him from having thumped on wine casks in his father's inn to determine the quantity of liquid therein. In his honor Austria issued a postage stamp in 1937.

An Ancient Tranquilizer

Consider the course of the stars as if you were driving through the sky and kept them company. Such contemplations as these scour off the rust contracted by conversing here below.—Marcus Aurelius



Meetings and Announcements

Oaks spring from acorns, yes—but not overnight.—Forbes Epigrams

FEBRUARY

American Academy of Allergy, [E], Statler-Hilton, Boston, February 3-7, Exec.-Sec.: Mr. James O. Kelley, 756 N. Milwaukee St., Milwaukee 53202.

American Academy of Occupational Medicine, Marriott Twin Bridges Motel, Washington, D. C., February 7-9. Exec. Sec.: Bertram D. Dinman, M.D., Institute of Industrial Health, University of Michigan Medical Center, Ann Arbor, Mich. 48104.

American College of Physicians (Air Force Regional), San Antonio, Tex., February 15-17 Info.: Lt. Gen. Richard L. Bohannon, USAF, (MC), The Surgeon General, USAF, Pentagon Bldg., Washington, D. C. 20330.

American College of Physicians (Alabama Regional), Point Clear, Ala., February 23-24. Info.: Howard L. Holley, M.D., U. of Alabama Medical Center, 1919 7th Ave. S., Birmingham, Ala. 35233.

American College of Physicians (Northern California/Nevada Regional), Monterey, Calif., February 16-17. Info.: Roberto Escamilla, M.D., 897 Hyde St., San Francisco, Calif. 94109.

American College of Physicians (Southern California Regional), Palm Springs, Calif., February 23-25. Info.: W. Philip Corr, M.D., 3660 Arlington Ave., Riverside, Calif. 92506.

American College of Physicians (Delaware Regional), Wilmington, Del., February 24. Info.: A. Henry Clagett, Jr., M.D., 515 W. 18th St., Wilmington, Del. 19802.

American College of Physicians (Hawaii Regional), Honolulu, February 21. Info.: Morton E. Berk, M.D., 1133 Punchbowl St., Honolulu 96813.

American College of Physicians (Kansas Regional), Topeka, Kan., February 23. Info.: Sloan J. Wilson, M.D., U. of Kansas Medical Center, Kansas City, Kan. 66103.

American College of Physicians (Nebraska Regional), Lincoln, Neb., February 3. Info.: Henry J. Lehnhoff, Jr., M.D., 720 Doctors' Bldg., Omaha, Neb. 68131.

American College of Physicians (Ohio/Western Pennsylvania, West Virginia Regional), Cincinnati, February 23-24. Info.: Richard W. Vilter, M.D., Cincinnati General Hospital, Cincinnati 45229.

American College of Psychiatrists, Fontainebleau Hotel, New Orleans, February 2-3. Sec.-Gen.: J. Martin Myers, M.D., 111 N. 49th St., Philadelphia, 19139.

American College of Radiology, [M], Drake, Chicago, February 6-10. Exec. Dir.: William C. Stronah, LL.B., 20 N. Wacker Dr., Chicago 60606.

American College of Cardiology, [E], San Francisco Hilton Hotel, San Francisco, February 28-March 3. Exec. Dir.: William D. Nelligan, 9650 Rockville Pike, Bethesda, Md. 20014.

The Minnesota Symposium on Prevention in Cardiology. Reducing the Risk of Coronary and Hypertensive Disease. May 2nd and 3rd, 1968, Mayo Clinic, Rochester, Minnesota. Sponsored by: The Minnesota Heart Association, The Mayo Foundation and The University of Minnesota. Information available from: Henry Blackburn, M.D., Stadium Gate 27, University of Minnesota, Minneapolis, Minnesota 55455.

L. E. Phillips Psychobiological Research Divisions of North Memorial and Mount Sinai Hospitals with The Minnesota Heart Association Symposium on Heart and Emotions. North Memorial Hospital auditorium, April 7, 1968. Afternoon and evening sessions (1:15 p.m. to 8:45 p.m.), with dinner being served at 5:30 in the hospital dining room. Attendance has been approved by the Academy of General Practice for 6 hours of Post-Graduate Study. Since the number of registrants will be limited, they will be accepted by acknowledgment in the order received. A Symposium for nurses will be held in the morning. Additional information may be obtained by calling Ralph Rossen, M.D., 588-0616, extension 301, or 339-1692, extension 596.


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(Continued on Page 323)

Law and Medicine

Complicating Developments in the Law of Criminal Responsibility

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Minneapolis, Minnesota

In recent decades the law of criminal responsibility in the United States has greatly modified the McNaghten test laid down more than a century ago** in England. Liberalization of that test has also brought some complicating developments.

New Hampshire in 1869 became the first American Jurisdiction to depart from the McNaghten rule.†

Irresistible Impulse Introduced Into the Federal Courts

In 1897 *Davis v. United States*# utilized the inability to distinguish between right and wrong together with what amounted to an irresistible impulse rule.

Matheson v. United States‡ in 1913 foreshadowed future developments in the charge to the jury to acquit if the crime "was the direct result or offspring of insanity."

The A.L.I. Rule

In 1953 the American Law Institute began a study which culminated in the drafting of a model Penal Code.

§4.01 provides:

(1) a person is not responsible for criminal conduct if at the time of such conduct as a result of mental disease or effect he lacks substantial capacity either to appreciate the criminality of his conduct or to conform his conduct to the requirement of law.

(2) . . . mental disease defects do not include an abnormality manifested only by repeated criminal or otherwise antisocial conduct.

§4.08(1) provides for mandatory commitment upon acquittal under these rules.

The Durham Rule

Finally in 1954 the District of Columbia substantially reiterated New Hampshire law in *Durham v. United States*§: a defendant may be considered innocent of a crime by reason of insanity if it can be demonstrated that the defendant was suffering from a mental defect at the time of the commission of the crime and, if so, whether the crime was a product of such mental disease or mental defect.

The *Durham* test for the first time gave psychiatrists the opportunity to characterize a defendant's psychology in unitary terms rather than within the narrow scope of distinguishing between right and wrong.

*New York Bar, the District of Columbia Bar and the Minnesota Bar.

**See Smith, B.: Background and Meaning of the McNaghten Case. Minnesota Med 50:1917, 1967.

†State v. Pike, 49 N.H. 399 (1869).

#Davis v. United States, 160 U.S. 469, 16 S.Ct. 353, 40 L.E. 499 (1895); 165 U.S. 373, 17 S.Ct. 360, 41 L.E. 750 (1897).

‡Matheson v. United States, 277 U.S. 540, 33 S.Ct. 355, 57 L.E. 631 (1913).

§Durham v. United States, 214 F.2d 862 (1954).

Mandatory Commitment in The District of Columbia

Thereafter Congress enacted D.C. Code §24-301(d), providing mandatory confinement in a mental hospital for anyone acquitted by reason of insanity. The stated sincere purpose of the act was to safeguard the public. It was admitted in subsequent senate hearings on the subject that there was a widespread fear that the defense of insanity would be resorted to unscrupulously by criminals who would then go scot-free.*

As a matter of fact, hearings before the senate subcommittee on constitutional rights of the mentally ill in 1961 disclosed that the number of acquittals on the ground of insanity did indeed increase,** aided by the rule of the Federal District Courts that the government must prove sanity beyond a reasonable doubt where the defendant introduces only "some evidence" of insanity.†

Release of the Committed Defendant

Section 24.301(d) provides for release of a committed defendant who has wholly recovered and is no longer dangerous to himself or others. The *Ragsdale* case# in 1960 imposed upon defendant the obligation to show by the preponderance of evidence that he was free from an abnormal mental condition and stated that any reasonable doubt was to be resolved against the defendant. It was held in *Overholser v. Russell* in 1960 that the "danger to himself or others" of the D.C. Code need not be physical or a crime of violence, but "any criminal act."‡

Prosecution Introducing Evidence of Defendant's Insanity

Inevitably defendants began to avoid the defense of insanity in the District of Columbia. At the same time the prosecution began to introduce evidence of insanity on its own initiative. An example of this was *United States v. Kloman*,§ in which the defendant pleaded not guilty to assault of a policeman. Defendant was committed under Section 24.301(a) of the D.C. Code for pretrial mental examination to determine competency. Eventually he was returned to court as competent to stand trial. At the trial the prosecution argued that defendant was not guilty by reason of insanity. (Defendant claimed justification as a defense.) He was committed following a verdict of not guilty by reason of insanity.

Reluctant Acquittal

The question of reluctant acquittal was considered in *O'Beirne v. Overholser*:£ There defendant had been acquitted of petty larceny as insane. He was thereupon committed and remained so for 3½ years longer than the maximum sentence for petty larceny. At the same time he brought habeas corpus. His diagnosis had been sociopathic personality disturbance. At the time of his commitment to St. Elizabeth's Hospital the official position of that institution was that sociopathy was not a mental disease. While he was an inmate the official position changed to record sociopathy as a mental disease. Therefore the certificate of the superintendent that defendant was wholly recovered and not dangerous was denied on the ground that the patient was a sociopath. On appeal the denial of the certificate was held arbitrary and capricious because of the change of classification of defendant's mental condition, which was not considered a disease at the time of his trial and acquittal.

The Supreme Court Curtails Reluctant Acquittal

In *Lynch v. Overholser*¶ defendant had been acquitted of check forgery on grounds of insanity. His offer to plead guilty was rejected by the trial judge, who entered a not-

*Constitutional Rights of the Mentally Ill. Hearings before the subcommittee on Constitutional rights of the Committee on the Judiciary, United States Senate, 87th Congress, 1st Session. U.S. Government Printing Office, Washington, 1961 at 385.

**Ibidem at 391.

†First Davis case, supra; Douglas v. United States, 99 U.S. App. D.C. 232, 239 F.2d 52 (1956).

#Ragsdale v. Overholser, 281 F.2d 943 (C.A.D.C., 1960).

‡Overholser v. Russell, 281 F.2d 943 (1960).

§United States v. Kloman, Crim. No. 383-58 D.C.D.C., (Feb. 15, 1960).

£O'Beirne v. Overholser, 287 F.2d 133 (C.A.D.C., 1961).

¶Lynch v. Overholser, 369 U.S. 705, 82 S. Ct. 1063, 8 L.E.2d 211 (1961).

guilty plea because defendant had been committed for pretrial examination to determine his competency. He had been found competent to stand trial, but it was considered "advisable to have further treatment" because he might "have relapses in the future." On the basis of the hospital report the Court refused the guilty plea. Thereupon and over his strenuous objection defendant was acquitted and committed. On appeal the Supreme Court avoided the constitutional questions. The Court held that the action of the trial judge was in error because the purpose of the statute was to protect against abuse of the *Durham* test whereby defendants might otherwise have gone free on easily obtained insanity acquittals. Public protection from dangerous individuals was held not to be a statutory purpose. These could be civilly committed. The Court ordered the defendant released unless civil commitment was commenced within ten days as provided by D.C. Code Section 21-310.

Lynch Decision Avoids Constitutional Issues

The Court did not consider the constitutionality of the commitment provision. Its statement of legislative purpose was at variance with the D.C. Court of Appeals in *Overholser v. Leach,** which stated that the primary purpose of the commitment provision was to protect the public from those who have committed criminal acts. The question was not whether the defendant was committed as innocent, because the verdict not guilty by reason of insanity most definitely was not an affirmative finding of present insanity; the verdict had the effect of including the defendant in a special class requiring hospitalization and treatment: ". . . there exists some rational basis for believing that the defendant suffered from a mental disease or defect of which the criminal act is a product," *Ragsdale v. Overholser.* An issue with which the Supreme Court in *Lynch* nowhere adequately dealt is the disparity between a finding of the jury or court relative to the defendant's state of mind during the commission of a particular act and commitment to a mental hospital on an indefinite basis without a finding of present insanity, as the District of Columbia Circuit has intimated.** This appears to be an unconstitutional deprivation of liberty which could readily be remedied by the institution of civil commitment proceedings following acquittal on the grounds of insanity, as English law now provides.†

The Currens Test Enunciated in the Third Circuit

In *United States v. Currens*# Chief Judge Biggs enunciated for the Third Circuit a rule similar to the *Durham* test. The new rule requires acquittal if a disease of the mind is shown and "the disease had so weakened his capacity to conform his conduct to the requirement of the law which he is alleged to have violated that he lacks substantial capacity to conform his conduct to the requirements of that law."

The Chief Judge distinguished his rule from that of the *Davis* case alluded to above, in which the test of irresistible impulse referred to control over conduct in question rather than to the more general conception of loss of willpower.

Other Circuit Courts Re-formulate Rules of Criminal Competence

Since *Currens* other Circuit Courts of Appeals have re-formulated rules of criminal responsibility. The Tenth Circuit essentially adopted the A.L.I. rule but changed the word *appreciate* to *know* in (1) of that rule.‡ The Second Circuit adopted the A.L.I. rule.§ The Eighth Circuit attempts to reconcile the A.L.I.

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*Overholser v. Leach, 103 U.S. App. D.C. 289, 257 F.2d 667 (C.A.D.C., 1960).

**Ragsdale, supra, note 8 at 947.

†Under the Criminal Lunatics Act of 1800 and the Trial of Lunatics Act of 1883 a defendant acquitted by reason of insanity in England ("guilty but insane") was remanded to custody "at his majesty's pleasure," i.e., for an indefinitely long period with no right to release. Halsbury's Statutes of England, Second Edition, Vol. 44 at 157. In 1964 this was amended to provide commitment as for the mentally ill in civil cases. The Criminal Procedure (Insanity) Act 1964 (c. 84) s.5.

#United States v. Currens, 290 F.2d 751 (C.A. 3, 1960).

‡Wion v. United States, 325 F.2d 420 (C.A. 10, 1963); cert. den., 377 U.S. 946, 84 S.Ct. 1354, 12 L.E. 2d 309.

§United States v. Freeman, 357 F.2d 606 (C.A. 2, 1966); United States v. Malafronte, 357 F.2d 629 (1966).

and McNaghten tests.*

Trend Among the States to Alter the McNaghten Test

These decisions reflect a trend among the states to alter the McNaghten test either by statute** or by judicial decision.† As things stand, a defendant may on identical evidence be acquitted by reason of insanity in the Second, Third or Tenth Circuit but convicted elsewhere. When the District of Columbia alone had adopted the *Durham* rule, no conflict existed since this was essentially a matter of legislation local in nature. Inasmuch as a split of authority now exists among the Circuit Courts of Appeal, the Supreme Court may feel compelled to consider the question of criminal responsibility for all the federal courts.

Prerequisites for Anomalous Assertion of Insanity by the Prosecution

The bizarre development in the District of Columbia, assertion of insanity by the prosecution, required more than a liberalized rule of criminal competence. Two additional predisposing conditions were: mandatory commitment upon acquittal by reason of insanity and a rule that sanity must be proved once evidence of defendant's insanity is introduced.

In Nebraska# as in the District of Columbia introduction of evidence of insanity shakes the presumption of defendant's sanity. Commitment upon acquittal by reason of insanity is mandatory too. But Nebraska follows the

*Duskey v. United States, 295 F. 2d 743, 759 (C.A. 8, 1961), cert. den., 368 U.S. 992, 82 S.Ct. 625, 7 L.Ed. 2d 536; Feguer v. United States, 302 F.2d 214, 245 (1962), cert. den., 371 U.S. 872, 83 S.Ct. 123, 9L.Ed. 2d 110. The Court preferred to "build upon . . . McNaghten and . . . irresistible impulse," utilizing three elements: cognition, volition and defendant's capacity to control behavior.

**Illinois: Chapter 38 Illinois Revised Statutes, Division I. Criminal Code of 1961, Title II, Article 6 §6-2: A.L.I. rule.

Once evidence of defendant's insanity is introduced, the presumption of sanity no longer prevails; burden of proof of sanity then devolves upon the state. People v. LeMay, 35 Ill. 2d 208, 220 N.E. 2d 184 (1966).

Upon acquittal by reason of insanity the fact finder must find whether "defendant has recovered from his former condition of insanity." Title VI §§115-3, -4 as amended by Act approved August 11, 1965.

If not found to have recovered, the court must thereupon commit to a mental hospital for a period not to exceed 12 months; defendant then becomes in all respects subject to §§8-12 of the Mental Health Code for civil commitment of the mentally ill, including discharge at the discretion of the head of the institution. Article 118, §118-2.

Maine: Maine Statutes ch 149 §38-2, added by Laws 1961, ch 310: Durham test.

Maryland: Md. Ann. Code, Art. 59, §9(a): A.L.I. rule. If in the court's discretion defendant should be confined following acquittal by reasons of insanity, the proceeding is as for civil commitment, Md. Ann. Code, Art. 59, §11.

Missouri: Mo. Stat. Ann. (1963), C.552, §552.030, sub§1.: A.L.I. rule in substance. Sub§5.: there is a conclusive presumption of criminal responsibility unless substantial evidence to the contrary is presented; burden of proof by a preponderance of evidence is upon defendant.

Montana: Laws of Montana (1967), C. 196, §95-501: A.L.I. rule. §95-508(2): defendant must be committed upon acquittal by reason of criminal non-responsibility, an affirmative defense for defendant to establish by a preponderance of evidence, §95-503(2).

New York: July 1, 1965: §1120 N.Y. Penal Law c. 40: "A person is not criminally responsible if at the time of such conduct as a result of mental disease or defect he lacks substantial capacity to know or appreciate either

(a) the nature and consequence of such conduct

(b) that such conduct was wrong."

This effects no substantial departure from the McNaghten test.

Vermont: Vermont Stat. Ann., Title 13, §4801: A.L.I. rule. Commitment upon acquittal as non-responsible is discretionary with the court, §4805.

Virgin Islands: Title 14, Virgin Islands Code, §14(4): all persons are "capable" of crimes except

(1) children under the age of seven years;

(2) children over the age of seven years and under the age of fourteen years, in the absence of clear proof that at the time of committing the act charged against them they knew its wrongfulness;

(3) idiots;

(4) persons who are mentally ill and who committed the act charged against them in consequence of such mental illness; and

(5) persons who committed the act or made the omission charged under an ignorance or mistake of fact, which disproves any criminal intent.

The above changes were suggested by Third Circuit Court of Appeals Chief Judge Biggs, who wrote the opinion in Currens, supra.

†Connecticut: State v. Davis, 146 Conn. 137 (1959). To be the subject of punishment an individual must have the "mind and capacity, reason and understanding enough to enable him to judge of the nature, character and consequence of the act charged against him, that the act is wrong and criminal, and that the commission of it will justly and properly expose him to penalty."

Kentucky: Terry v. Commonwealth, 371 S.W.2d 862, 864-5 (1963): A.L.I. rule adopted in substance. After acquittal by reason of insanity the court may impanel a jury to decide whether defendant is presently of unsound mind, in which case he is confined until restoration of sanity. Russell's Kentucky Practice, RCr 9.90(2).

Massachusetts: Commonwealth v. McHoul, 226 N.E.2d 556 (1967): A.L.I. rule adopted. The burden is on the Commonwealth to prove defendant mentally responsible for the crime, Commonwealth v. Johnson, 188 Mass. 382, 74 N.E. 939, Commonwealth v. Clark, 292 Mass. 409, 198 N.E. 641. Introduction of evidence of insanity shakes the presumption of sanity, Commonwealth v. Cox, 327 Mass. 609, 100 N.E.2d 14(1951). Commitment of defendant as mentally ill after acquittal by reason of insanity is discretionary with the trial judge. Ann. Laws Mass. C278, §13.

Wisconsin: State v. Shoffner, 31 Wis. 2d 412, 143 N.W. 2nd 458 (1966). Defendant may elect to be tried under the A.L.I. rules if he accepts the burden of proof. This rule was admittedly adopted "as an experiment." (Shifting the burden of proof was a concession to the dissenting judges.) Should the defendant not accept this burden, he would be strictly entitled only to a charge under the McNaghten rule.

District of Columbia: McDonald v. United States, 312 F.2d 847(1962). The District Court here amplified the definition of mental disorder under the Durham test to include any abnormal condition of the mind which substantially effects mental or emotional processes and substantially impairs control over behavior.

In its opinion the court compared the other existing rules of criminal competence as follows:

McNaghten: cognition only

Durham: no standards for jury with respect to causation; irresistible impulse rule applied in the United States district courts too narrow to apply except in situations amounting to an explosive fit.

Wion: wording of A.L.I. rule changed from "appreciate" to "know."

Currens: substantial capacity to conform only: that part of the rule deleted which concerned appreciation of wrongfulness.

#Forske v. State, 123 Neb. 161, 242 N.W. 404(1932).

McNaghten rule.

In Michigan* and Oklahoma** commitment upon acquittal by reason of insanity is mandatory, but defendant has the burden of introducing evidence sufficient to raise a reasonable doubt; some evidence is not sufficient.

In Georgia,† Minnesota,# Nevada‡ and Ohio§ commitment is mandatory upon acquittal by reason of insanity; but defendant must prove insanity as an affirmative defense.

New Hampshire, home of the *Durham* test prior to its promulgation in the District of Columbia, makes commitment upon acquittal by reason of insanity discretionary with the court rather than mandatory.£ So does Massachusetts, which follows the A.L.I. rule.

Wisconsin makes commitment mandatory following acquittal by reason of insanity¶ but offers defendant the opportunity to be tried under the A.L.I. test only on condition that he assume burden of proof of insanity.[1]

Illinois meets the three conditions of mandatory commitment upon acquittal by reason of insanity, burden of proof of sanity once evidence of defendant's insanity is introduced and a liberal test of criminal competence, the A.L.I. test.

Thus, of the states here considered only Illinois provides the framework for anomalous assertion of insanity by the prosecution.

No Federal Statute Provides for Commitment After Acquittal by Reason of Insanity

A quite contrary situation exists in the federal criminal courts other than the District of Columbia: there is no federal statute providing for commitment of a defendant acquitted by reason of insanity.[3]

Perhaps Congress will react to the spread of more liberal rules of criminal competence among the Circuit Courts of Appeal as it did to *Durham*: fearing a deluge of acquittals by reason of insanity, it provided for mandatory commitment.

At present in the Second, Third and Tenth circuits defendant is aided not only by more liberal rules of criminal competence but also by the universal rule of the federal courts that the government must prove sanity beyond a reasonable doubt once some evidence of defendant's insanity is presented.

Deluge of Acquittals Avoidable in More Than One Way

Mandatory commitment upon acquittal by reason of insanity is not the only means of averting a deluge of such acquittals. Wisconsin achieved this result by shifting the burden of proof of insanity onto defendant.

Anomalous Assertion of Insanity by the Prosecution Can Be Avoided in Several Ways

Anomalous assertion of insanity by the prosecution has been laid to rest by *Lynch* in the federal courts. In the state courts New Hampshire avoids this threat by making discretionary with the court commitment following acquittal by reason of insanity.

Texas[4] avoids the threat of anomalous assertion of insanity by the prosecution while it solves the constitutional problem intimated in *Ragsdale* and evaded in *Lynch*. It does this simply by separating criminal guilt and the need for commitment to protect the public or treat the defendant psychiatrically. In case the defense of insanity is raised, the jury is asked to find whether defendant was insane[5] at the time of the alleged offense and whether insane at the time of the trial. If found insane at the time of the offense but sane at the time of the trial, he is set free.

If found insane at the time of the offense and insane at the time of the trial, commitment is mandatory, but defendant is treated as any other non-criminal patient committed for an indefinite period.

---

*People v. Finley, 38 Mich. 482 (1878).

**Gallagher v. State, 81 Okla. Crim. 15, 159 P.2d 562 (1945); Maas v. Territory, 10 Okla. 714, 63 Pac. 960 (1901).

†Carroll v. State, 204 Ga. 510, 50 S.E.2d 330 (1948).

#Bonfanti v. State, 2 Minn. 123 (1858).

‡State v. Clancy, 38 Nev. 181, 147 Pac. 449 (1915).

§State v. Colley, 78 Ohio App. 425, 65 N.E.2d 159 (1946).

£N.H. Rev. Stat. Ann. §607:3 (Supp. 1959).

¶Wisconsin Statutes Annotated §957.11 (3).

[1]State v. Shoffner, supra, note †, p. 320.

[2]See note**, p. 320.

[3]Commitment as incompetent before trial is covered by 18 U.S.C.A. §§4 244, -5. Commitment as insane after conviction is covered by 18 U.S.C.A. §§4241.

24 U.S.C.A. §211 does not provide for commitment upon acquittal by reason of insanity. It is inapplicable because ". . . it pertains solely to persons found to be insane, a finding which . . . cannot be made under existing federal criminal procedure." Sauer v. United States, 241 F.2d 640 at 651-2, n. 32(C.A. 9, 1957), citing 17 Op. Atty. Gen. 211 (1881).

[4]Vernon's Texas Statutes Annotated Art. 46.02 Sec. 1, 2, 3.

[5]Regrettably, Texas' test of criminal competence, essentially NcNaghten, Ex parte Hodges, 166 Cr.R. 433, 314 S.W.2d 581 (1958), does not match the adroit modernity of its criminal procedure in this area.

Conclusion

Developments in the law of criminal competence in the United States, while producing more liberal tests, have also resulted in complications. Some jurisdictions have, nevertheless, demonstrated that it is possible to provide more liberal tests of criminal competence while safeguarding against abuse and constitutional infirmity.

The Aftereffects

One day a patient with a long since healed leg fraction came to a Leningrad hospital. His leg was seven inches shorter than normal. A bony growth projected from the bone at the point of the fracture. The patient walked with crutches. Two improperly knit and shortened halves remained instead of the hip-bone. A part of the bone, reduced to fragments, had been extracted during the bone-setting operation.

The knit parts of the bone had to be disjoined and a bone plate taken from some other limb inserted between them. But a seven-inch-long bone plate was not all. The hip had to be strong enough to bear the weight of its owner, and a transplanted bone fragment could scarcely be expected to have such strength.

So the doctors decided to lengthen the leg to its natural length without implanting a bone fragment. Professor Bogoraz, a prominent Soviet surgeon, had proposed a most original method, and they were going to try it on their patient. It was an operation known as segmental osteotomy.

The improperly knit shortened bone is cut into oblique segments—two in the case of the top section of the broken bone, and two in the case of the other. If one of the sections is longer than the other, it may be cut into three segments. The doctors then use a special device to draw out the leg gradually to its normal length. The segments of the bone are pulled apart by the muscles, their oblique surfaces gliding one along the other. The upper end of one segment forms a continuation of the other's bottom end, forming a continuous chain of bone segments. A bony growth forms at their points of contact, joining them together for good.

An operation of this kind was performed on the patient, and a month later he was discharged from the hospital. His gait was firm. He left his crutches behind in the clinic.*

*L. Fridland, M.D.: The Achievement of Soviet Medicine, 1961 edited and translated from the Russian by W. Horsley Gantt, M.D.

The Imaginary Line

The point of demarcation between normality and abnormality is purely an imaginary line sketched for the sake of convenience. As a youngster I had to reckon with the fact that a herd tightly bunched could not properly graze. I had to realize that there could be leaders and stragglers widely separated. And I had to learn to distinguish between those cattle forming the outer fringes of a fanned-out herd, and those deliberate strays heading off toward the corn fields. It was strangely similar to the eternal problems confronting the psychiatrist.*

*James Fisher, M.D.: A Few Buttons Missing, 1951.

All governments are obscure and invisible.—Bacon

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There are six vessels that lead to the Feet, three to the Right and three to the Left. They reach down to the Soles of the Feet.

There are four vessels to the Liver which convey to it Moisture and Air.

There are four vessels to the Intestines and to the Spleen which likewise convey Moisture and Air. There are two vessels to the Bladder which convey the Urine.

There are four vessels which end in the Rectum. They give and bring forth in it Moisture and Air. Afterwards they turn towards the Rectum, each vessel to the Right and Left side right down to the Feet, mixing itself with the excrement.

*Bryan, Cyril: The Papyrus Ebers, D. Appleton and Company, New York, 1931, p. 124-127.

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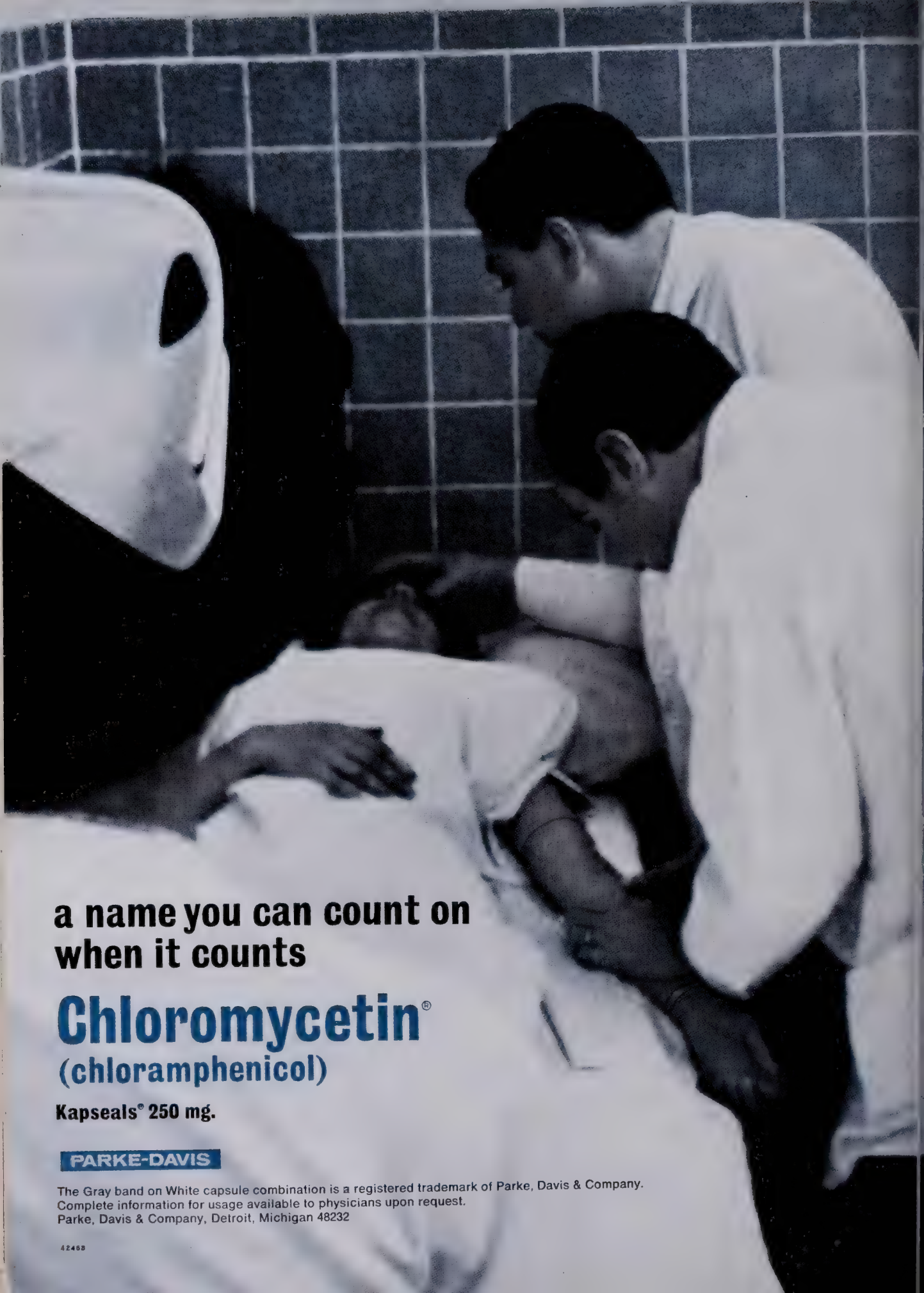
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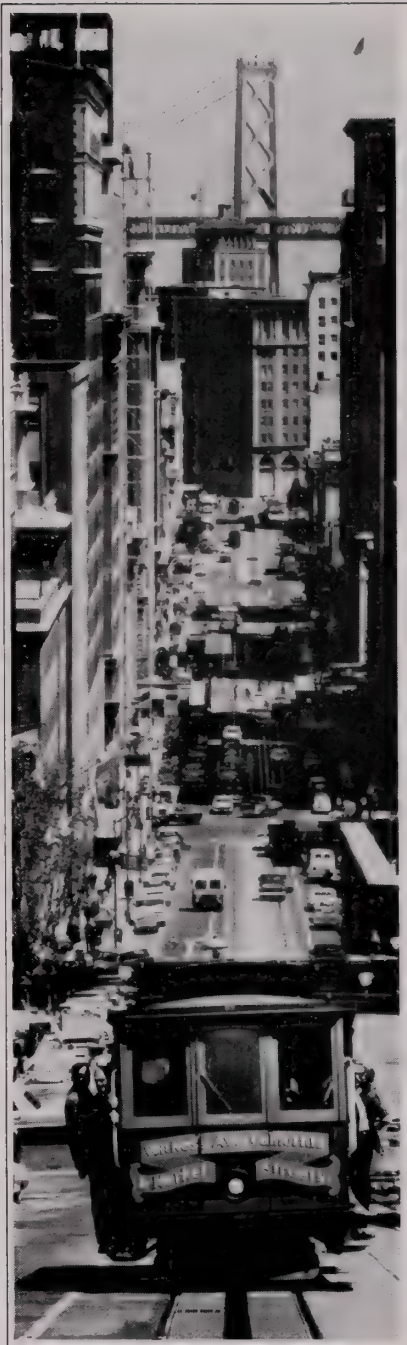
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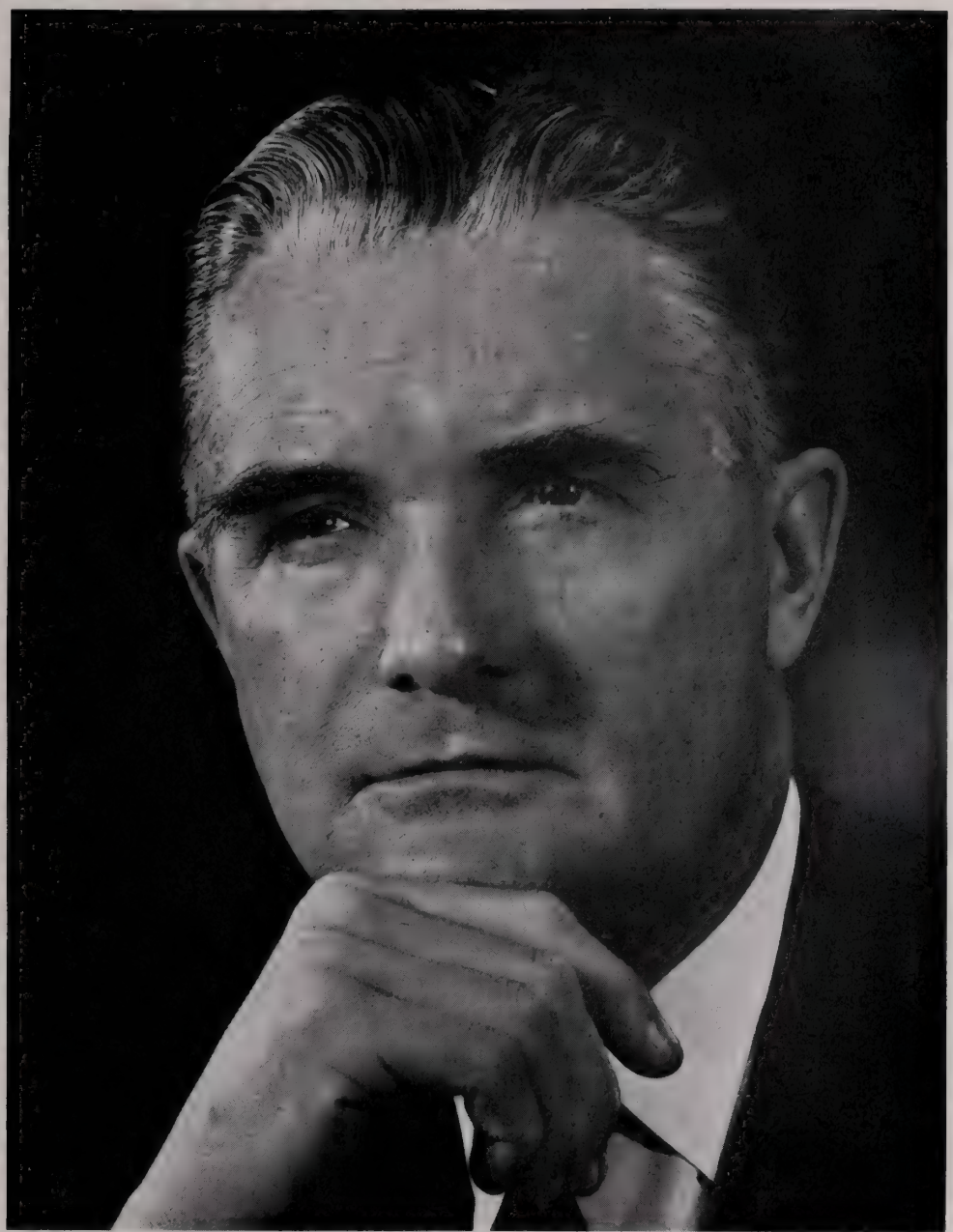
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President's Letter

How Many Surgeons Are Needed?

THERE HAS BEEN concern that our greatly expanded residency training programs are producing too many surgeons for the needs of our Minnesota communities.

Competition among surgeons can and should be beneficial to the ones utilizing their services: the referring physicians and their patients. When the surgeons are willing to subjugate the occasional unethical competitive urge, then the many advantages of a healthy competition become obvious.

Perhaps one of the earliest results of an abundance of personnel in a professional area is the effort of its members to become more highly trained. More years in a better training program permit of more attractive stature in the arena. The pursuit of excellence among surgeons must certainly bring obvious benefits to the recipients of their skill.

The creed of all physicians dictates a maximum effort and full devotion to the task of healing, and when competition serves to sharpen the intensity of the effort it is safe to say that this has been of value to the patient.

As their number increases, more of the newly well-trained surgeons find satisfaction, interesting activity and prosperous living in the smaller metropolitan communities. The general practitioner and internist in these cities no longer find it necessary to send their surgical patients away or to rely upon the part-time, partial services of the itinerant surgeon.

As the modern surgeon becomes more extensively trained he is perforce less well trained in other areas of medicine, and he therefore does not seek to build his specialty from a broad-based beginning in a general medical practice, but rather remains restricted to his own area of competence. This is one of the many benefits which accrue to the patient.

Abundance of general surgeons also has a tendency to gradually increase the ranks of the surgical sub-specialists and in turn to bring a greater supply of specialized talent and training to these areas.

As long as the competitive influence among the abundant supply of young surgeons promotes professional excellence and high competence, the health and welfare of the patient will be served. An over-supply of good surgeons is not foreseeable—except possibly in the distant future.

J. H. Strickler, M.D., President
Minnesota Surgical Society

The butterfly is the Fact—gleaming, fluttering, settling for an instant with wings fully spread to the sun, then vanishing in the shades of the forest. Whether you believe in Free Will or Predestination all depends on the slanting glimpses you had of the colour of his wings.—*Winston Churchill—Amid These Storms*

Acumen

The skillful doctor knows by observation, the mediocre doctor by interrogation, the ordinary doctor by palpation.—Chang Chung-ching (170-196)

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Encephalopathy and Fatty Degeneration of the Viscera

Reye's Syndrome

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NECROPSY FINDINGS of encephalopathy and fatty degeneration of the viscera (Reye's syndrome) in a three-year-old boy, who survived a month after onset of his illness, stimulated a search of the literature in order to learn of other physicians' experience with this syndrome and to attempt to answer some of the questions which had been raised in our minds by the circumstances surrounding this case.

A review of the literature disclosed that the syndrome in children characterized by encephalopathy and fatty degeneration of heart, liver, and kidneys had first been reported in 1929 from England, in a study of six cases: five patients alive and one dead at the time of the report.[1] Thirty-four years later, in 1963, six reports of this syndrome appeared in the world literature containing a total of 68 cases: seven patients alive at the time of the reports and 61 dead.[2-7] The reports of Reye, Morgan and Baral[2] and Anderson[3] from Australia in that year had awakened an interest in physicians in England, Scotland, South Africa and New Zealand who had seen similar instances in their practices. In 1964, six additional fatal cases were added from Czechoslovakia.[8] In 1965, the United States literature reported the first seven cases from this country, all terminating fatally.[9-12] Three reports in 1966 from Czechoslovakia,[13] New Zealand,[14] and Scotland[15] added a total of 35 new cases, all with fatal terminations. The most recent report of five additional cases, one fatal, was from the Massachusetts General Hospital in 1967.[16] These 16 reports since 1929 have recorded 127 cases, with 16 patients alive and 111 dead at the time the authors wrote their papers.

Clinical Features

Age Incidence

The patients' ages have ranged from four months to 13 years, with the majority of

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cases occurring at about two years of age.

Initial Symptoms

The clinical features of the syndrome, described by Reye and his colleagues,[2] have not changed. The initial period of the illness includes malaise, cough, sore throat, earache, or rhinorrhea, in varying combinations. Usually one week after onset, but occasionally two to three weeks later, abrupt and severe vomiting occurs, followed by a semi-comatose state, and occasionally convulsions.

Physical Findings

Most patients have an abnormality of respiratory rate or rhythm. About half have a palpable, large, or firm liver. Muscle tone and tendon reflexes tend to be changeable; about ¾ of the patients had increased or variable muscle tone and tendon reflexes, about ½ had abnormal or equivocal plantar reflexes, and about one third had a characteristic posture with flexed elbows, extended legs, and clenched hands.

Laboratory Data

Clinical laboratory abnormalities are often encountered in the blood sugar, cerebrospinal fluid sugar, blood urea nitrogen, serum glutamic-oxalacetic acid transaminase (SGOT), and the differential white blood cell count.[2] The blood sugar is usually low. In Reye's group there were seven low blood sugar values; six patients had less than 50 mg.%, one patient had less than 62 mg.%, one had two reports of normal values and one had a hypoglycemia of 195 mg.%. Other investigators have confirmed this hypoglycemic tendency.[5,14,15] One group[5] emphasized that the hypoglycemia was not affected by glucose infusion.

The cerebrospinal fluid sugar was reduced to less than 25 mg.% in 13 of 19 patients.[2]

Blood urea nitrogen exceeded 40 mg.% in 75 per cent of the cases,[2,15] but marked elevations, above 50 mg.%, were unusual.[2,3,14] The serum glutamic-oxalacetic acid transaminase was estimated in only seven cases, all of which showed elevations ranging from 106 to 1170 Karmen units per ml. per minute.[2]

Bacterial and viral studies, when performed, were usually negative.

In Simpson's study,[15] the most common acid-base disturbance was metabolic acidosis, often associated with respiratory alkalosis due to hyperventilation. Simpson reported six patients with a pH range from 6.85 to 7.47.

Electroencephalographic Findings

Reye, Morgan and Baral[2] reported electroencephalographic abnormalities in this syndrome. All the patients studied had gross and generalized changes.

Etiology

Viral and toxic etiologies have been postulated without proof. Becroft,[14] in a detailed speculation, also postulated that nutritional, endocrine, and genetic factors might be important. He concluded, as others had, that the etiology is unknown.

Treatment

Symptomatic therapy, with attempts to correct inadequacies of ventilation and to combat hypoglycemia and acid-base alteration, has been employed.

Pathologic Findings

Gross

In all instances the findings at necropsy have been similar. Grossly the brain is edematous and swollen with flattening of the cerebral convolutions. The liver is slightly enlarged, firm, and yellow. The kidneys and myocardium have a slightly yellowish hue.

Microscopic

Microscopically the brain tissue changes are nonspecific and neuronal. The neuronal cells may be swollen or shrunken and deep-staining. The cerebral capillaries and small vessels have fat-filled endothelial cells. Inflammatory changes are absent.

Fat-filled parenchymal cells are found in a diffuse, uniform distribution in the liver, in the muscle fiber of the heart, and in the proximal convoluted tubules and proximal loops of Henle of the kidneys.

Report of a Case

Presenting Complaint

An apparently healthy 35-month-old white boy was

admitted to St. Mary's Hospital in Duluth on December 6, 1965, with a history of having been well until one day before admission. He had vomited five or six times during the day. About three hours prior to admission, he had had trouble clearing his throat, which his father thought was "dry heaves." Then the boy had become flaccid and unresponsive and was brought to the hospital.

Past History

The child had had no previous surgery, trauma, or serious illnesses, and careful questioning elicited no history of allergy or drug ingestion. No other member of the family was ill.

Initial Physical Findings

The boy was comatose on admission, his temperature was 98.6° (F.) and his breathing was labored. He appeared well developed and well nourished and his skin was clear. The pupils were equal, regular, and reacted to light and accommodation. The nose was patent. The lungs, after aspiration of the tracheobronchial tree, were clear. The heart was normal; no enlargement or murmur was found. The abdomen was soft; neither liver nor spleen was palpable. Neurologic examination disclosed an absent gag reflex, symmetrical tendon reflexes, with a questionably positive right Babinski. He responded to painful stimuli and exhibited no posture characteristic of a known disease.

Laboratory

Laboratory values on admission disclosed a hemoglobin level of 13 Gm., a white blood cell count of 58,000 with 15% nonsegmented neutrophils, 57% segmented neutrophils, 23% lymphocytes, and 5% monocytes. The blood urea nitrogen was 28 mg.%, the serum sodium 139 mEq /L, the serum potassium 5.4 mEq/L, the serum chlorides 102 mEq/L, and the serum carbon dioxide content 27.1 mEq/L. The urine had a specific gravity of 1.017, was negative for sugar and acetone, showed a trace of albumin and 0-1 white blood cells, and a rare red blood cell per high-powered field. A blood culture, drawn on admission, was reported negative after 14 days' incubation. Cerebrospinal fluid was under normal pressure; cultures and smears of the fluid were reported negative for pathogens. The spinal fluid protein level was 19 mg. %; no cells were found.

Progress Report

Six hours after admission, respiratory embarrassment necessitated a tracheostomy. A chest x-ray the first day, after tracheostomy, showed changes compatible with bilateral bronchopneumonia. Examination at that time showed the patient to be in a semistuporous state with bilateral positive Babinski signs.

During the three days following admission the patient's state of consciousness gradually improved. A brain scan with 125 microcuries of Hg^{203} showed an essentially normal pattern two days after admission. On the third hospital day, an electroencephalogram (without prior sedation) was considered "probably normal." Blood sugar was 72 mg.%. Parenteral fluid therapy during the first four days included glucose and electrolyte replacements. The tracheostomy tube was removed on the fifth day after admission.

Over the next 28 days the patient gradually improved except for persistence of an ataxic gait. However, his hand coordination was not affected, for he could put together a jig-saw puzzle.

Because of the long period of disability, the presence of ataxia, and the possibility of a brain tumor existing, pneumoencephalography was performed on the 33rd hospital day. Preoperative atropine (1/300th grains) was given 80 minutes prior to induction. The procedure, done under sodium pentothal anesthesia (700 mgm. rectally before anesthesia and 400 mgm. intravenously) without difficulty, showed that no air was delivered to the ventricular system. The subarachnoid space was well visualized and showed increased depth and width of the sulci, suggesting a moderate degree of atrophy.

Following the pneumoencephalography, the patient was sent to the Intensive Care Unit for post-anesthetic observation. Continuous drowsiness persisted and, 23 hours after the procedure, acute deterioration was obvious. Examination showed a lethargic patient with a respiratory rate of 60/minute and a heart rate of 160/minute. Respirations became Cheyne-Stokes in type and the heart tones became inaudible. There was no response to resuscitative measures and the patient died 24 hours following the pneumoencephalogram.

Necropsy Findings

Gross

Necropsy was performed four hours after death. No remarkable, grossly detectable discoloration was seen in the heart. The liver weighed 680 grams and was diffusely yellow. The kidneys appeared normal. The brain

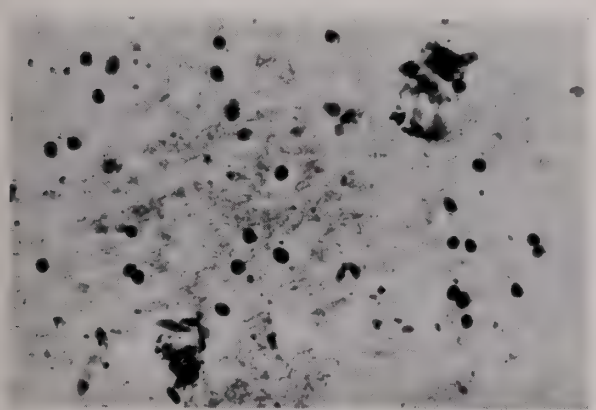


Fig. 1—Oil red 0 stain showing fat in endothelial cell of brain vessels.

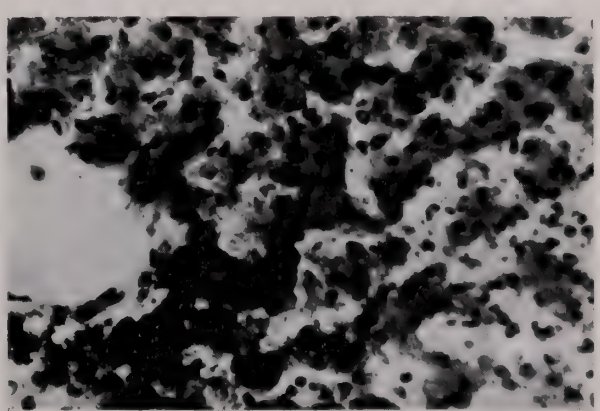


Fig. 2—Oil red 0 stain showing fat in liver cells.

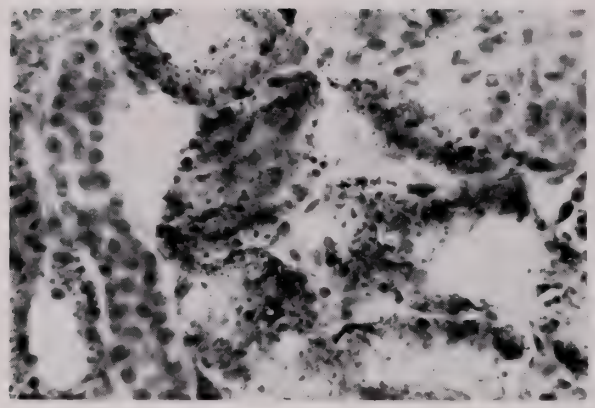


Fig. 3—Oil red 0 stain showing fat in proximal tubules of the kidney.

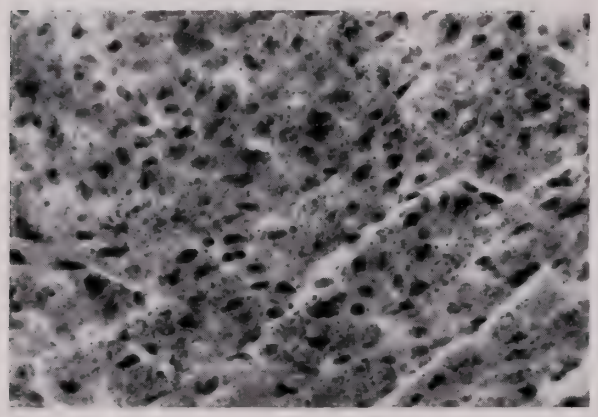


Fig. 4—Oil red 0 stain showing diffuse particulate fat in the myocardium.

weighed 1330 grams and showed narrowed sulci and broad, flattened gyri in close approximation. A coning defect was present in the cerebellar tonsils. (This undoubtedly resulted from increased intracranial pressure, and the resultant herniation was the cause of death.) Transection of the cerebral hemispheres disclosed no tumor, hemorrhages, or infarction. There were no other pertinent, significant gross findings.

Microscopic

Histologic examination showed petechial pontine hemorrhages; fat-stains of the brain revealed capillary endothelial cells containing fat (Figure 1). A few neurons were swollen, while others were contracted and showed an increase in basophilic staining. Special stains of the liver also showed diffuse fatty change (Figure 2). The proximal tubules of the kidney showed similar fatty change (Figure 3). Finely dispersed, fatty fiber infiltration was found in the heart (Figure 4). A specimen of blood, drawn at postmortem examination, was negative when cultured.

Comment

Although the laboratory and autopsy findings in this patient are similar to those reported in the literature, his course differed from the course of the usual victim of this syndrome in the unusually long duration of illness and in the finding of the fatty degeneration 33 days after the onset. One patient, who was reported to have survived this syndrome, had a specimen of liver taken for biopsy three weeks after the acute episode, and this tissue was histologically normal.[2] This case seems to be the first with fatty degeneration and encephalopathy that retained the histologic fatty feature for an extended period of time.

Another feature worthy of serious consideration is illustrated by the patient's rapid decline after sodium pentothal anesthesia. Sedation with barbiturates may be dangerous in patients with encephalopathy and fatty degeneration.

Summary

The clinical, biochemical, and pathologic changes of the syndrome of encephalopathy and fatty degeneration of the viscera (Reye's syndrome) are reviewed with two new observations: one, persistence of fatty degenerative changes for over a month after the onset, and second, rapid deterioration and death after barbiturate anesthesia.

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5-16 May be secured from the author or the reprints.

The nations which have put mankind most in their debt have been small states—Israel, Athens, Florence, Elizabethan England.—Dean Inge

The Surgical Fate of Ureteral Calculi

Lithotomy or Manipulation?

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A CALCULUS in the ureter threatens the functional and anatomic integrity of the kidney and at times the life of the patient. In most instances, the calculus must be removed by spontaneous passage, cystoscopic manipulation, or ureterolithotomy.†

There are a number of factors to be considered in determining the course of management (Table 1). The size and location of the calculus within the ureter are perhaps the most important; however, there are other prerequisites that also influence the decision. Calculi, 0.5 cm. in greatest diameter or smaller, demonstrating progressive movement down the ureter, causing little or no pain and without significant obstruction or infection, might reasonably be expected to pass spontaneously. The decision to await spontaneous passage is a difficult one. Close observation is mandatory in the event of emergency, and facilities should be available for immediate cystoscopic manipulation or ureterolithotomy. The patient who has chronic renal disease or a solitary kidney and harbors a ureteral calculus may be in extreme danger, and to await spontaneous passage may be life-threatening.

The prerequisites for selection of conservative management are also applicable in determining the need for definitive surgical treatment. Once it is determined that the calculus is incapable of spontaneous passage, the alternatives must be carefully considered.

To choose ureterolithotomy or cystoscopic manipulation of a ureteral calculus is not a question of which method is technically easier to perform, but which is in the best interest of the particular patient under consideration.

With this in mind we have reviewed a successive group of patients with ureteral calculi, in whom the treatment was either ureterolithotomy or cystoscopic manipulation, in an

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†See Test Your Word Score Page 375.

TABLE 1
Factors in Management of Ureteral Calculi

Location
Degree of obstruction
Size of stone
Presence of infection
Severity of pain
Associated renal disease, e.g., solitary kidney, renal insufficiency
Length of stay in ureter
History of spontaneous passage

TABLE 2
Presenting Signs and Symptoms in 81 Patients With Ureteral Calculi

Sign or symptom	Patients
No symptoms	4
Pain only	61
Renal colic	57
Other symptoms (bachache 1, vaginal 1, buttocks 1, suprapubic 1)	4
Pain and symptoms of infection	6
Pain and gross hematuria	2
Painless hematuria	4
Anuria	1
Frequency, nocturia, and urgency	2
Fever	1
Total	81

TABLE 3
Size and Site of Calculi in 36 Patients Undergoing Ureterolithotomy

	Calculi by site in ureter			
Size, cm.	Upper third	Middle third	Lower third	Total
<0.5	0	1	1	2
0.5-0.9	7	2	0	9
1.0-2.0	13	9	5	27
>2.0	1	0	0	1
Total	21	12	6	39*

*Three patients had two calculi each.

TABLE 4
Postoperative Complications in 36 Patients Undergoing Ureterolithotomy

Complication	Patients
Prolonged urinary drainage	10
Wound infection	1
Thrombophlebitis	1
Bacteremia	1
Gross hematuria (7 days)	1
Acute gout	1
Total	15 (42%)

effort to more clearly define the guidelines that influence the decision regarding definitive management.

Our Series

Ninety-five consecutive patients with a diagnosis of ureteral calculus underwent definitive surgical treatment, either cystoscopic manipulation or ureterolithotomy, or ureterolithotomy combined with other upper urinary-tract surgery. In this last group with combined procedures, there were 14 patients, including six with combined pelviolithotomy and ureterolithotomy, six whose stone disease required nephrectomy with either partial or subtotal ureterectomy, and one patient with bilateral ureterosigmoidostomies, in whom the ureteral calculus was detected at the time of urinary diversion. In one patient the calculus was found in the stump of a ureter. These 14 cases were not considered suitable for evaluation.

Findings

Ureterolithotomy or cystoscopic manipulation of the ureteral calculus was the primary treatment in the 81 patients. Patients' ages ranged from 11 to 78 years, and males predominated in a ratio of 4 to 1. The peak incidence was in the fourth and fifth decades. The calculus displayed no preference for the right or left ureter.

The presenting signs and symptoms for the entire group of patients with ureteral calculi are seen in Table 2. The majority of patients presented with some form of pain, principally that of renal colic. Four patients were asymptomatic, and these required ureterolithotomy because of associated chronic renal disease significantly aggravated by the presence of a calculus.

Ureterolithotomy was the selected form of management in 36 of the 81 patients. Thirty-nine calculi were removed; three patients had two calculi each. The relationship of calculus size to location in the ureter is shown in Table 3. Thirty-seven of the 39 calculi were 0.5 cm. in diameter or larger; only nine of these 37 calculi were less than 1.0 cm. Only six calculi situated in the lower third of the ureter required ureterolithotomy; five of these were at least 1.0 cm. in diameter. Thirty-three of the

39 calculi removed by ureterolithotomy were in the upper and middle thirds of the ureter.

Postoperative complications developed in 15 of the 36 patients (Table 4). The most frequent complication was prolonged urinary drainage through the drain site (10 of 15 patients). There was no relationship between method of closure of the ureterotomy incision and prolonged drainage.

Forty-five patients with ureteral calculi were deemed suitable for cystoscopic manipulation (Table 5). One calculus, 0.7 cm. in greatest diameter, was successfully extracted from the middle third of the ureter. The remaining 44 calculi were located in the lower third. Manipulation was attempted on only one calculus larger than 2.0 cm. in diameter, and this was unsuccessful. The majority of calculi in this group were less than 1.0 cm., although seven of nine calculi 1.0 cm. or larger were successfully extracted. Attempted cystoscopic manipulation of a ureteral calculus was successful in 38 of 45 patients, a success rate of 84%.

Complications after successful cystoscopic manipulation of 38 calculi included two patients with renal colic secondary to blood clot, one patient with transient bacteremia, and one with acute pyelonephritis.

Attempted cystoscopic manipulation was unsuccessful in seven of 45 patients. Subsequent ureterolithotomy was carried out 48 to 72 hours after attempted manipulation on four patients (Table 6). The one patient with ureteral perforation, which occurred secondary to manipulation, was managed by immediate ureterolithotomy. The one whose ureteral calculus passed spontaneously 48 hours after attempted manipulation might reasonably be considered a successful result of cystoscopic manipulation; however, since the calculus was not extracted at manipulation, it is not counted as such.

Discussion

There are advantages and disadvantages accompanying the selection of either method of calculus removal. However, there are useful guidelines which may serve to minimize the subsequent morbidity known to be associated with either technique. The enthusiastic use of one method to the exclusion of the other is to be condemned. An intelligent appraisal of the prerequisites for cystoscopic manipulation or ureterolithotomy is in the best interest of the

TABLE 5

Size and Site of Calculi and Outcome of Cystoscopic Manipulation in 45 Patients With Ureteral Calculi

	Calculi by site in ureter				Extraction	
Size, cm.	Upper third	Middle third	Lower third	Total	Successful	Not successful
<0.5	0	0	17	17	13	4
0.5-0.9	0	1	18	19	18	1
1.0-2.0	0	0	8	8	7	1
>2.0	0	0	1	1	0	1
Total	0	1	44	45	38 (84%)	7 (16%)

TABLE 6

Subsequent Management of Seven Patients Who Underwent Cystoscopic Manipulation

Subsequent procedure	Patients	
Ureterolithotomy		4
Calculus, <0.5 cm.	1	
Calculus, 1.5 cm.	1	
Calculus, 1.0 cm.	1	
Perforation of ureter	1	
Nephroureterectomy (staghorn calculus, pyelonephritis, ureteral calculus—1.0 cm.)		1
Spontaneous passage of 0.4 cm. calculus 2 days after manipulation		1
Calculus (0.2 cm.) left; no further treatment (asymptomatic)		1
Total		7 (16%)

patient.

Successful cystoscopic manipulation of a ureteral calculus in 84% of the patients was accompanied by a minimal morbidity, whereas ureterolithotomy was associated with a significant morbidity rate. The difference is reflected in the average time of hospitalization for patients in each group (Table 7). When ureterolithotomy was performed, patients could be expected to remain in the hospital an average of five days longer than patients undergoing successful manipulation, if no complications resulted; or an additional 11 days with associated complications. Successful cystoscopic manipulation, even when accompanied by complications, increased the in-hospital time by only 2.6 days.

TABLE 7
Average Time of Hospitalization (Days)

Group	Without complications	With complications
Successful manipulation (38 patients)	6.4	9
Ureterolithotomy (36 patients)	11.4	17.8

Calculi that are located in the upper or middle third of the ureter and that fail to descend are usually larger than 0.5 cm. in diameter; and when associated with persistent subjective and objective findings, these calculi should be removed by ureterolithotomy. Similarly, calculi situated in the lower third of the ureter and greater than 1.0 cm. in diameter will probably require ureterolithotomy, although an initial attempt at cystoscopic manipulation should be considered, and at times such manipulation may be successful.

Cystoscopic manipulation should be considered for all calculi 1.0 cm. or less in greatest diameter, if located in the lower third of the ureter, since such calculi may be confidently extracted in most instances. Calculi larger than 1.5 cm. usually will not be suitable for manipulation. Patients known to have associated chronic renal disease, previous renal or ureteral surgery, or a solitary kidney are more likely to require ureterolithotomy. In this series, 29 of the 36 patients requiring ureterolithotomy gave a history of acquired and congenital abnormalities or of recurrent urinary-tract calculi. Of the 45 patients requiring cystoscopic manipulation of a ureteral calculus, only 11 revealed a significant history of renal disease. The results of cystoscopic intra-ureteral extraction of ureteral calculi compared favorably with other reported series.[1-3] Successful extraction of the calculus may be confidently expected in at least 80% of patients, provided the necessary prerequisites for attempting manipulation are satisfied. Similarly, postoperative morbidity can be expected to be significantly less with manipulation than with ureterolithotomy. In this series, successful cystoscopic manipulation was accompanied by a hospital stay of 6.4 days as compared with 11.4 days for patients with ureterolithotomy.

An inflexible attitude that favors either method of calculus removal seems unwarranted, because suitable guidelines do exist for the appropriate selection of either method.

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If you think you think, ask yourself what is the greatest thought you ever thought, then listen to the silence.—Origin Unknown

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In youth, time passes at a pace that often is annoyingly slow; in middle-age, it takes on speed, and in old age it goes jet.—Chilton (Wisconsin) Journal

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Physicians, like beer, are best when they are old.—Thomas Fuller

Coronary Arteriography

Selective vs. Non-selective Methods

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CORONARY ARTERIES were first visualized in man using contrast materials in 1945.[1] Since then various methods have been introduced to visualize the coronary vessels. Non-selective coronary arteriography has been generally unsatisfactory because of the inconsistency in coronary arterial filling despite prodigious† flooding of the root of the aorta with contrast material. A review of 1000 thoracic aortograms at the University of Minnesota Hospitals[2] using a single injection of contrast material through a large bore catheter showed wide variation in coronary artery filling. Various methods employed to reduce cardiac output temporarily or inject contrast material during diastole[3,4] not only have proved hazardous but have not produced adequate visualization of the coronary vessels[5,6,7,8,9,10] according to present-day standards.

In our experience the loop or ring catheter with multiple side holes positioned in the aortic root just above the aortic valve has proved the most satisfactory non-selective method of coronary arteriography. Recently we have studied twelve patients by non-selective and selective arteriography. The comparative value of the root aortogram utilizing a ring catheter vs. the selective coronary arteriogram form the basis of this report.

Materials and Methods

One hundred twenty-two patients had bilateral selective coronary arteriograms. Of these patients, 12 had an additional aortogram using a ring catheter. The method of selective catheterization — percutaneous transfemoral—has been reported previously.[2,11] Five of the twelve patients had an aortic root injection by means of a ring catheter since it was not possible to cannulate the right coro-

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†See Test Your Word Score Page 375.

nary ostium. At a later date each of these five patients was studied by a selective right coronary arteriogram.

The right coronary artery and two major branches of the left coronary artery—the left anterior descending and the left circumflex branch—were graded separately. The selective and non-selective arteriograms were graded independently. Each vessel was graded on the basis of filling and opacification as follows:

Excellent filling,	4+	
Good filling,	3+	
Fair filling,	2+	
Poor filling,	1+	
No filling,	0	(zero)

Results

Root aortography in this group of patients produced only "fair" or "poor" visualization of the coronary arteries. However, there was "good" to "excellent" opacification of the right coronary artery in five patients (Table).

By selective angiography there was excellent filling of the coronary vessels in the majority of patients studied.

Case Report

A 46-year-old white married male complained of palpitations unrelated to exertion for four years. As a child he had had "pneumonia" but did not give a history of rheumatic fever. There was no history of angina pectoris, syncope, or congestive failure. Physical examination revealed a blood pressure of 130/78 mm. Hg.; the pulse was 80 and regular. The heart was not enlarged. There were a grade 2/6 systolic ejection murmur at the aortic area and a faint early blowing diastolic murmur at the lower left sternal border.

The routine blood and urine studies as well as the chest x-ray, electrocardiogram and vectorcardiogram were normal. The Master's test was negative. The aortic valve region appeared calcified at fluoroscopy.

Angiography

Right heart catheterization revealed all pressures in the right atrium, ventricle and pulmonary artery to be normal. The cardiac output (Fick method) was 3.64 L/min. at rest; with exercise the output rose to 5.30 L/min. The left ventricular pressure was 152/8. The end diastolic pressure did not change significantly during exercise. There was no evidence of mitral insufficiency during left ventricular angiography. There were a 28 mm. Hg. systolic gradient across the aortic valve and mild aortic insufficiency noted during thoracic aortography using a ring catheter with multiple side holes (Figure 1).

Interpretation

Mild poststenotic dilatation of the ascending aorta was noted. The right coronary artery, the left anterior descending branch of the left coronary artery and the left circumflex branch of the left coronary artery were partly visualized (Table, Patient No. 1). Several areas in the coronary arterial system were thought to be narrowed

TABLE

Visualization of Coronary Arteries by Non-Selective and Selective Angiography

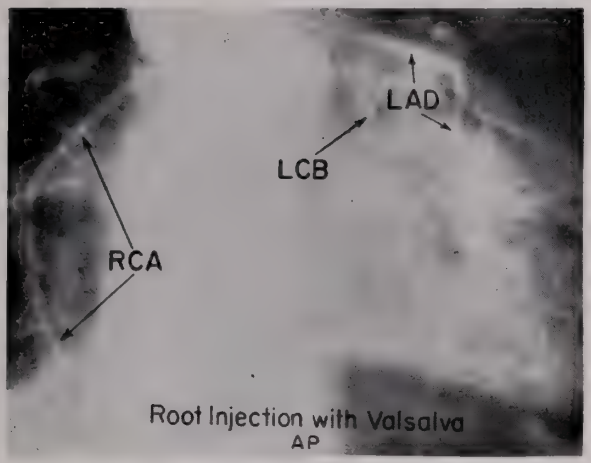
	Patients			Root Aortogram			Selective Coronary Arteriogram		
	Age	Sex	Diagnosis	LAD	LCB	RCA	LAD	LCB	RCA
1.	46	M	Congenital AS* Mild AI**	1+	1+	2+	4+	4+	4+
2.	54	M	RHD***, AI	2+	1+	3+	4+	3+	4+
3.	55	F	AI, Cause not known	2+	2+	3+	4+	4+	4+
4.	50	M	RHD, AI	1+	1+	2+	4+	4+	4+
5.	38	M	RHD, AS, AI	2+	2+	2+	3+	4+	4+
6.	42	M	Marfan's syndrome	0	0	1+	4+	4+	4+
7.	49	M	Congenital AS, AI	2+	1+	3+	4+	4+	4+
8.	36	M	CAD****	3+	2+	4+	4+	4+	4+
9.	42	M	CAD	2+	2+	2+	3+	4+	4+
10.	54	M	CAD	1+	2+	2+	4+	4+	4+
11.	59	M	CAD	2+	1+	3+	4+	3+	4+
12.	48	M	CAD	2+	2+	2+	4+	4+	4+

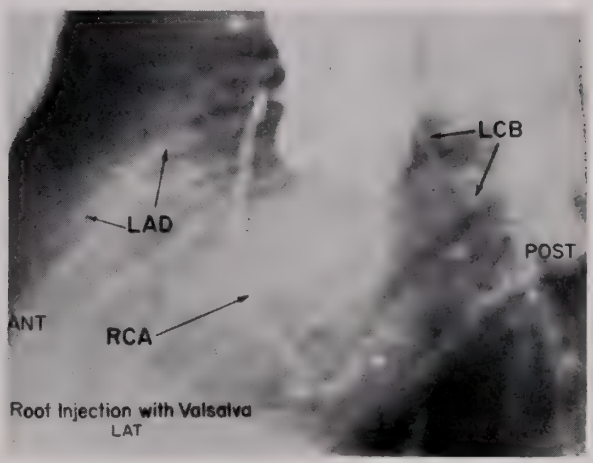
* Aortic stenosis

** Aortic insufficiency

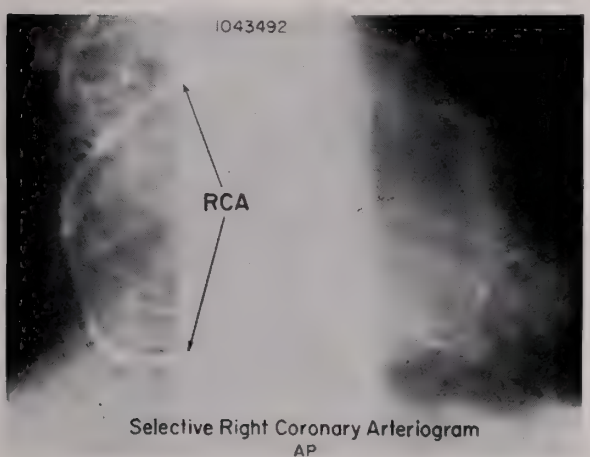
*** Rheumatic heart disease

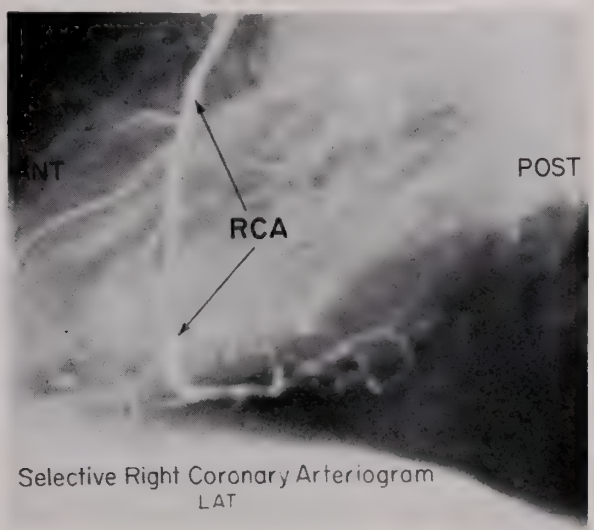
**** Coronary artery disease

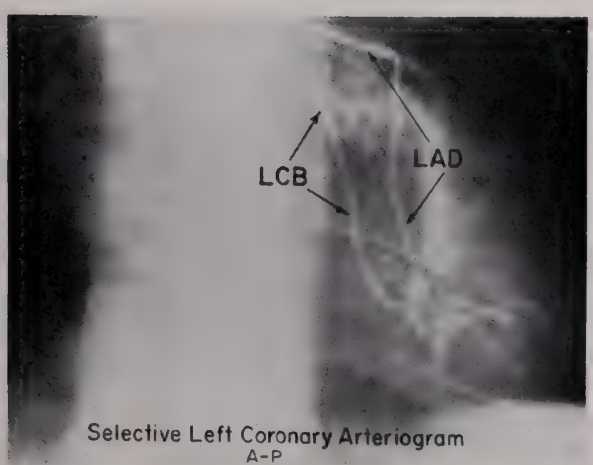


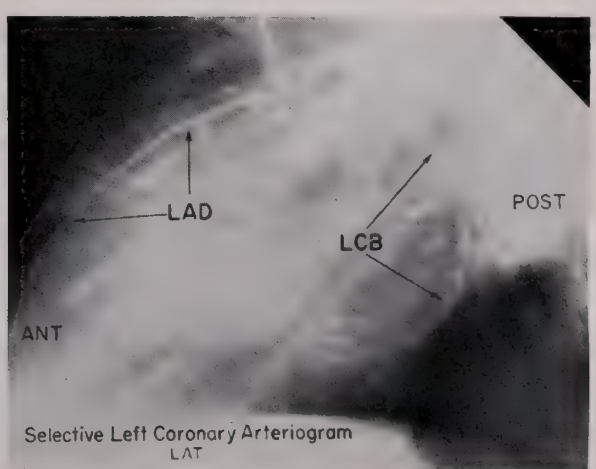


Figures 1—Note that the coronary arteries are visualized but despite the use of the ring catheter and prolonged Valsalva, the anatomical detail is poor. The right coronary artery is seen more clearly than the left anterior descending and the left circumflex branches. Both the left anterior descending and the left circumflex branches appear to be diffusely narrowed using this technique.









Figures 2—There is excellent filling of the right coronary artery, left anterior descending branch and left circumflex branch. All large coronary vessels appear normal.

by atherosclerotic plaques. Because of this a selective coronary arteriogram was performed three days later showing completely normal coronary arteries (Figure 2).

Comment

In our hands bilateral selective coronary arteriography is possible in 95% of patients studied and is consistently superior to non-selective root aortography in defining coronary artery anatomy and pathology. It is not possible in many cases to adequately opacify all major coronary branches by aortography. In a study by Sones and Shirey adequate visualization of the coronary arteries was possible in less than 70% of the patients studied by aortography.[12]

The clinician and radiologist are frequently misled by the thoracic aortogram. What appears as segmental coronary narrowing by aortography is frequently found to be normal either by selective coronary arteriography or at necropsy. Conversely there may be more coronary lumen narrowing demonstrated by selective coronary arteriography or at necropsy[13] than was suspected from the aortic root study. We have seen at our institution three patients who were thought to have severe coronary narrowing on the basis of a root aortogram. However, at necropsy they were found to have only minimal coronary narrowing. We feel that the root aortogram is misleading in some cases because of inadequate filling of coronary vessels and in other cases because of "layering" of contrast material.

Selective coronary arteriography has been helpful in other situations where non-selective aortograms have been of little value. Coronary anastomoses have been demonstrated in 25% of the patients studied.[11] Coronary arteriovenous fistulae and anomalous origin of the left coronary artery from the pulmonary trunk have been documented. In addition, selective angiography has shown more clearly anomalous distribution of coronary vessels—an important finding for the cardiac surgeon.

Conclusions

The risk of selective and non-selective coronary arteriography at our institution is the same.[11] We prefer selective coronary arteriography since it is the most accurate diagnostic method available today. Despite all these arguments in favor of the selective method there are groups[14] that find the non-selective coronary arteriography the method of choice.

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A fanatic is a man that does what he thinks the Lord would do if he knew the facts of the case.—Finley Dunne

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Disease

The diseases of the present have little in common with the diseases of the past save that we die of them.—Agnes Repplier

Nodules in the Substance of the Upper Lip

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NOT ONLY ARE nodules in the substance of the upper lip infrequent, but many surgeons tend to regard these lesions as inconsequential. As a result, such nodules may be hastily and inadequately removed, sometimes without subsequent microscopic examination. We have found that most nodules in the substance of the upper lip represent tumors which, if not properly excised, will readily recur even though they are benign; furthermore, if malignant, these growths are sometimes difficult to control. Another observation worthy of mention is that the tumors discussed in this paper, although rare in the upper lip, are much less common in the lower lip.

The literature on this subject is meager. Chaudhry and co-workers[1] found that there were 43 cases of benign tumors of the minor salivary glands at Minneapolis and St. Paul hospitals from 1939 to 1960. Of these 43 tumors, 40 were mixed tumors; three were located in the upper lip and none in the lower lip. These authors also reviewed the literature from 1924 to 1960; they discovered that of 733 mixed tumors in the minor salivary glands, 105 were in the upper lip and 13 in the lower lip. In addition, they found six cases of cylindroma† (adenoid cystic carcinoma) of the upper lip. Fine and associates[2] reviewed tumors of the minor salivary glands in the mouth and pharynx treated at the Henry Ford Hospital from 1916 to 1959. Of 42 benign tumors, 25 were mixed tumors; five of them were located in the upper lip. Furthermore, two cases of cylindroma of the upper lip were described.

In our study of nodules in the substance of the upper lip, the records of all patients with benign and malignant lesions of the upper lip seen at the Mayo Clinic from 1944 to 1963 inclusive were abstracted. However, those tumors that started in adjacent tissues and in-

*Mayo Clinic and Mayo Foundation: Section of Plastic Surgery.

**Mayo Graduate School of Medicine (University of Minnesota), Rochester: Resident in Plastic Surgery.

†See Test Your Word Score Page 375.

volved the upper lip by direct extension were excluded.

Surprisingly, only 36 patients with tumors located in the substance of the upper lip were encountered. However, the pathologic nature of these neoplasms was interesting (Table). It is evident that very few tumors in the substance of the upper lip are inconsequential. Mixed tumors, the most common benign growths will recur promptly unless adequately removed, and the malignant neoplasms all present serious problems.

TABLE
Distribution of 36 Patients With Upper-Lip Tumors

Type of tumor	No.	Per cent
Benign		
Mixed tumor	24	66.6
Mucous cyst	3	8.3
Inflammatory lesion	2	5.6
Malignant		
Cylindroma	4	11.1
Leukemic infiltrate or lymphoma	2	5.6
Metastatic carcinoma	1	2.8
Total	36	100.0

Benign Tumors

Mixed Tumors

Of the 24 patients with mixed tumor, 14 were males and 10 were females. The nodules in two patients were adherent to the skin, whereas in the remaining 22 the growths were located in the substance of the upper lip, unattached to the skin or mucosa. The average age of patients with mixed tumor was 52.5 years; 66.6% were between 30 and 59 years old. Although the duration of such a neoplasm often is difficult to determine, 75% of the patients had had their lesions from two to 15 years. In 21 patients in whom the size of the nodule was specified, the sizes ranged from 0.1 to 3 cm. Although such growths can be painful, usually they are symptomless, the patient complaining only of a lump or swelling in the lip. Two patients had a history of trauma which, no doubt, had nothing more to do with the tumor than call it to the patient's attention.

Usually a mixed tumor arises from the epithelial elements in salivary glands, but they may occasionally develop from similar cellular components in sweat glands. Such neoplasms generally are well encapsulated and they grow slowly. Microscopically, nests or strands of epithelial cells surrounded by a mucoid or chondroid stroma can be seen. Cartilage was present in three tumors.

In four of the 24 patients with mixed tumor, the tumor was recurrent; it had been excised prior to the patient's registration at the clinic. At our institution, treatment consisted of wide excision, with either primary closure of the wound or local plastic repair.

Analysis of the results of treatment revealed that only one patient was known to have a recurrence. This patient was observed but not treated at the Mayo Clinic. The patients were followed up for from two to 17 years; however, four patients were lost to follow-up.

The one patient who had a local recurrence was a 39-year-old woman. She had noticed a nodule in her upper lip. The nodule had been excised by her home physician prior to her first examination at the clinic, and the pathologist had reported that the growth was a cylindroma. This prompted her home surgeon to re-excise the involved region. Subsequently, the patient was seen at the Mayo Clinic where the slides of the previous excision were reviewed, and a diagnosis of benign mixed tumor was made but no treatment given. Five months later another tiny nodule appeared in the upper lip. However, the surgeon in the patient's home community elected not to remove it, and no further information was available.

Mucous Cyst and Inflammatory Tumors

Five patients had a lump in the substance of the lip. In three, the lump was near the mucosa, and the diagnosis was indeterminate clinically. On excision, however, the three submucosal nodules proved to be mucous cysts, and the other two lesions were found to be inflammatory.

Malignant Tumors

Cylindroma (Adenoid Cystic Carcinoma)

Four patients in our series, three women and one man, had a cylindroma in the upper lip. The ages of these patients ranged from 34 to 60 years, with an average of 48.2 years. The sizes of the lesions varied from 1 to 3 cm. When the four patients sought treatment at the Mayo Clinic, the lesions had been present 10

years, five years, six years, and five months, with an average of 5.7 years. The signs and symptoms were no different from those of patients with mixed tumor; the chief complaints were a lump or swelling and occasionally soreness or discomfort.

Microscopically, cylindromas have a honeycomb or Swiss-cheese type of cellular pattern. The cells are small and uniform in size, have dark nuclei, and are arranged in layers around cyst-like spaces that may contain mucus or hyaline material. Being poorly encapsulated, the tumors may show evidence of infiltration into the surrounding tissues.

All four patients had had some form of surgical intervention prior to examination at the clinic. In two patients, the lesion was explored and biopsied; in the remaining two, the growth was excised, one of them on two occasions. At this institution, two patients had their primary lesion treated by excision and electrocoagulation, one patient had electrocoagulation alone, and the fourth had interstitial irradiation in the form of radon seeds for a lesion that had recurred a second time.

Studies concerning the results of treatment revealed that two patients had metastatic lesions; one of these patients also had evidence of local recurrence.

In our experience, a cylindroma in any location is almost certain to recur in spite of having been widely removed. Although its growth is especially slow, this tumor is extremely serious; local recurrences and metastases, both regional and distant, are common, the lesions making their appearance anywhere from one to 10 years or more after the initial treatment. Pulmonary metastasis from cylindromas is a frequent complication of this disease and can be present for years without causing noticeable symptoms. We were surprised to find that two of the four patients with cylindroma of the upper lip were living 16 and 18 years after treatment of the primary tumor, with no apparent evidence of local recurrence or metastasis.

In one of the two patients with metastasis, both lung fields were involved, but there was no sign of recurrence of the primary lesion. The pulmonary lesions became evident 5 1/4 years after the initial treatment of the cylindroma in the lip. Unfortunately, this patient was lost to further study. In the other patient, the primary tumor recurred and metastatic lesions developed in regional lymph nodes below the body of the mandible five years after treatment of the primary tumor. The metastatic nodes were treated by interstitial radiation. Two months later, a metastatic lesion appeared in the left lung, and after an additional 15 months, the pulmonary metastatic nodule had grown eight times larger. This patient was a 34-year-old man who was still living seven years after the initial treatment.

Other Malignant Nodules in the Substance of the Upper Lip

The remaining three malignant nodules occurring in the substance of the upper lip in our series involved one leukemic infiltrate that occurred in a four-year-old boy with acute leukemia, one lymphoma in a patient who had malignant lymphoma of the cervical lymph nodes, and one metastatic carcinoma. In the patient with the metastatic carcinoma, the primary lesion occurred in the rectosigmoid colon and the metastatic lesion appeared three weeks after abdominoperineal resection.

Discussion

From the foregoing study, it seems evident that the presence of a nodule in the substance of the upper lip should not be regarded as unimportant; on the contrary, such a lesion is likely to be a tumor of some significance. In our series, about 86% of such nodules proved to be neoplasms that required careful surgical removal and microscopic examination. Of the total number, 78% were found to be mixed tumors or cylindromas.

A mixed tumor can be satisfactorily eradicated by surgical enucleation, carefully carried out so as not to cut into the lesion, since it is usually well encapsulated. Should the growth be more or less adherent to the skin or mucosa, the skin or mucous membrane immediately overlying the tumor should also be excised. Incomplete removal of the growth leads to recurrence; the recurrent lesion is many times more difficult to eliminate surgically than is the original lesion.

Twenty-four mixed tumors in the upper lip compared to only two in the lower lip were

seen at the Mayo Clinic from the years 1944 to 1963, inclusive. Why the upper lip should be a more common site for the development of such a lesion is uncertain, but possibly the reason is related to the more complicated embryologic development of the upper lip.

Cylindromas of the upper lip are rare, but the possibility that a nodule in the substance of this anatomic structure is a cylindroma should be borne in mind so that wide removal can be carried out at the initial surgery. The data on cylindroma described in this paper illustrate the tendency for a tumor of this type to grow and metastasize slowly; consequently, there is a definite need for follow-up examinations over a long period.

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Son (Harvey Cushing at Yale, 1887) to Father and Reply

"I have to again send a supplication to you for money. It seems as though you sent me just a day or two ago that $40 which, in making out my accounts last night, I find to be too small to pay my board bill for $12, which comes in every other Friday . . . I take the News—a daily which costs four dollars; it is almost a necessity as all the notices etc. are printed in it. I also take the Record, a biweekly for $1.50 and the Yale Literary Magazine for $3.00." Enclosed was an itemized expense account which included fifty cents for the "trunk to the depot," ten cents for carfare, twenty-five for breakfast, and twenty-five cents for a "chicken show."

A bone of contention was Harvey's participation in athletics. He was playing shortstop on the freshman baseball team, and when they were scheduled to play the Harvard freshmen, he wrote home for permission to play.

The reply came: "Dear Harvey, I will try to reply to your letter calmly, though I do feel sore and disturbed over the unhappy position you have brought us into. I carefully explained before you went to New Haven, that we were going into a partnership with mutual responsibilities and duties. I was to supply the means, and you to conduct yourself to my approval while the partnership survived. Among the conditions I insisted on, and which I understood you to assent to, were those that you would not smoke, drink or be guilty of any immoral conduct or join a College ball club or boat crew . . ."

However, the doctor relented somewhat by adding that if the boy could not withdraw gracefully from the Harvard game, he would do no more about it, but "that must be the end of that sort of thing absolutely and for good."

*Sarah R. Riedman: Masters of the Scalpel, 1962.

The Chin

Chins are exclusively a human feature, not to be found among the beasts. If they had chins, most animals would look like each other. Man was given a chin to prevent the personality of his mouth and eyes from overwhelming the rest of his face, to prevent each individual from becoming a species unto himself.—*Malcolm Chazal*

Big men become big by doing what they didn't want to do when they didn't want to do it.—*Insurance Salesman*

An Analysis of 4000 Chemistry Graphs

Comments on Disease Patterns

RICHARD L. REECE, M.D.*
Minneapolis, Minnesota

I SHALL SAY a word or two about a referral laboratory's experience with 4000 serum survey chemistry graphs. In a few years, chemistry graphs, now generated by some 200 multichannel analyzers across the country, will be available to most doctors. My aim here is to acquaint practicing physicians with the graphs —what they are, how they are created, how many abnormal tests they detect, and what patterns certain conditions give. I will emphasize patterns, for, by recognizing these, physicians can diagnose unsuspected diseases.

What Chemistry Graphs Are

Multiple Channel Autoanalyzers** simultaneously measure 12 serum substances and record their concentrations on a moving chart. Analyzers come in two types—a "Hospital Model" and a "Survey Model." Hospital models analyze for serum electrolytes and eight other serum components. Survey models run the same eight tests but substitute for electrolytes these tests: lactic dehydrogenase, glutamic oxaloacetic transaminase, inorganic phosphorus, and cholesterol (Figure 1). We use the survey model (Figure 2), and the data I shall present concerns only survey chemistry graphs.

How Graphs Are Created

How do multiple channel analyzers work? They operate on the principle of continuous flow analysis. Let me briefly summarize this process. The analyzer aspirates two or three millimeters of a serum specimen; splits it into 12 streams which flow through a series of parallel plastic tubes; separates by air bubbles samples in each stream; mixes the dozen moving rivulets with reagents; passes some of the mixtures over a semipermeable membrane

*Fellow, American Society of Clinical Pathology; Pathologist, Lufkin Medical Laboratories and Automated Medical Laboratory.

**Sequential Multiple Autoanalyzer (SMA-12, SMA-12/60), Technicon Corporation, Ardsley, New York.

which dialyzes out diffusible compounds; and pumps specimens to mixing coils or to heating baths where colors develop. Downstream, the 12 colored solutions move through a flow cell colorimeter which measures light absorbed by each color. Then a pen trailing red ink traces concentrations of all serum substances on a revolving chart. From this chart (a series of chemistry graphs separated by perforated lines) technologists tear off individual graphs, photostat them, and send originals to referring physicians.

How Many Abnormal Tests Graphs Detect

Among the 4000 specimens referred to our laboratory, 37.5 percent came from hospital patients, the rest from office patients. I mention types of patients because normal ranges and number of abnormal chemical tests will vary with the nature of the patient population. We mostly analyzed sera from patients with known or suspected disease—not from normal subjects in good health.

To arrive at normal ranges, we plotted the cumulative data for each test on gaussian* probability paper. This statistical method allowed us to calculate normal value data without testing large groups of normal subjects.[1] In Table 1, I list normal ranges estimated this way and record percent of abnormal tests. Table 2 indicates the number of normal graphs among the 4000 we produced. It also discloses the percent of graphs that had one, two, three, or four or more abnormal tests.

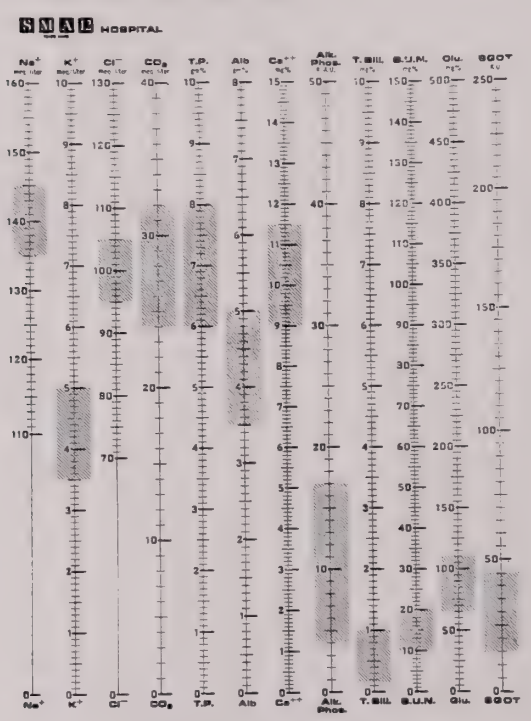
*See Test Your Word Score Page 375.

Disease Patterns

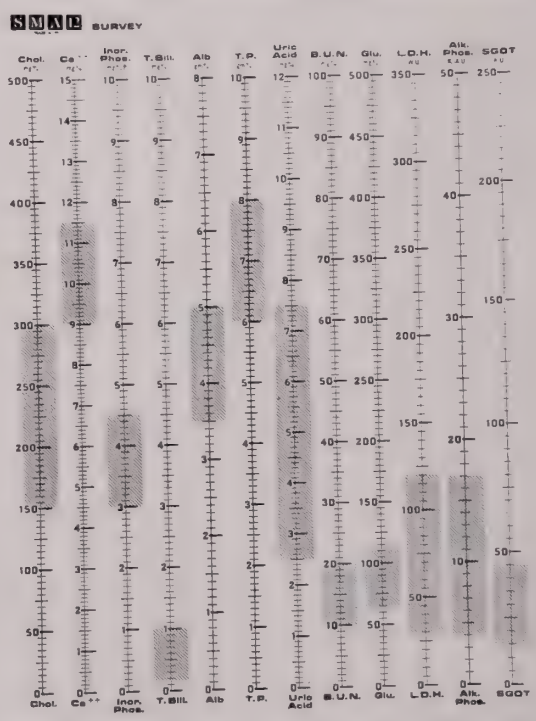
When a physician picks up a chemistry graph, he can quickly see what tests are abnormal. When two or more are abnormal, these sometimes form a pattern which may provide clues that will indicate what further information he should seek. Now I shall discuss certain conditions and show their graph patterns.

Pernicious Anemia

In pernicious anemia, marrow megaloblasts house large stores of lactic dehydrogenase, and red cells hemolyze more easily than normally. These factors probably cause serum lactic dehydrogenase to rise. In our series, I know of four cases of untreated pernicious anemia.



Chemistry Graph with electrolytes



Survey Chemistry Graph with cholesterol, inorganic phosphorous, uric acid, and lactic dehydrogenase instead of electrolytes.

Fig. 1—Two types of chemistry graphs produced by Sequential Multiple Autoanalyzers. The shaded bars indicate the normal range for each test.

TABLE 1

Tests	Normal Ranges: Probability curves	Normal Ranges: Values on Chemistry Graphs	Percent of Abnormal Tests: Low	Percent of Abnormal Tests: High
Cholesterol (Chol)	150-304	150-300	2.0	4.0
Calcium (Ca++)	8.7-10.7	9.0-11.5*	2.5	2.2
Phosphorus (Nor. Phos.)	2.6-4.5	3.0-4.5*	1.3	2.7
Total Bilirubin (T.Bili.)	0.2-0.8	0.2-1.0	....	5.2
Albumin (Alb.)	2.8-4.4	3.5-5.0	8.7	....
Total Protein (T.P.)	6.0-7.9	6.0-8.0	4.9	2.1
Uric Acid	2.5-7.6	2.5-7.5	....	11.0
Blood Urea Nitrogen (BUN)	8-25	10-20	0.5	9.2
Glucose (Glu.)	75-126	70-110	0.5	10.5
Lactic Dehydrogenase (LDH)	40-117	30-120	....	8.9
Alkaline Phosphatase (Alk Phos)	5-15	5-17		10.4
Serum Glutamic Oxaloacetic Transaminase (SGOT)	11-40	15-45	....	7.2

Abnormal tests among 4000 survey chemistry graphs. The percent of abnormal tests refers to those tests that were outside the normal ranges estimated on probability paper. *Recently, the Technicon Corporation announced that after "field trials," they are changing the normal range of calcium to 8.5 to 10.5 mg% and the normal range of phosphorus to 2.5 to 4.5 mg%.

In each, lactic dehydrogenase went off the upper end of the chart, i.e., levels exceeded 350 Wacker-units, and in each serum bilirubins hovered between 1.2 and 1.5 mg% (Figure 2).

Serum lactic dehydrogenase levels in pernicious anemia surpass those found in any other condition. Levels go up exponentially as hemoglobins fall, but enzyme values will rapidly decline when patients respond to B_{12}. After the physician starts B_{12}, he can expect serum lactic dehydrogenase levels to fall 50 percent in five days.[2]

One other patient whose serum we analyzed manifested a high lactic dehydrogenase and a slightly elevated bilirubin. She had a hemolytic anemia from a glucose-6-dehydrogenase defect. Hemolytic anemias of any cause will result in high lactic dehydrogenase levels. We recorded 12 other lactic dehydrogenases over 350 Wacker-units, but all sera had multiple other abnormal tests because patients had diseases such as myocardial infarction, liver necrosis, or metastatic tumor.

Although we have not seen graphs from definite cases, pulmonary embolism will almost always elevate serum lactic dehydrogenase and sometimes raise the serum transaminase and serum bilirubin. Amador and Potchen reported 41 patients who, by their symptoms, signs, and lung scans, had pulmonary emboli.[3] Forty of these showed high lactic dehydrogenases, while one half exhibited elevated

TABLE 2

Number and percent of normal and abnormal graphs among 4000 tested on Survey Sequential Multichannel Autoanalyzer.

	Number	Percent
Normal Graphs	2104	52.6
Abnormal Graphs		
one abnormal	1005	25.1
two abnormal	492	12.3
three abnormal	212	5.3
four or more abnormal	107	4.7
Total	4000	100.0

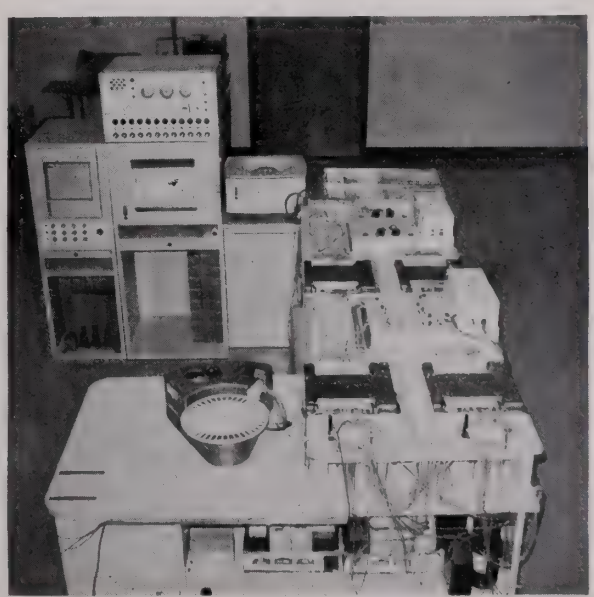
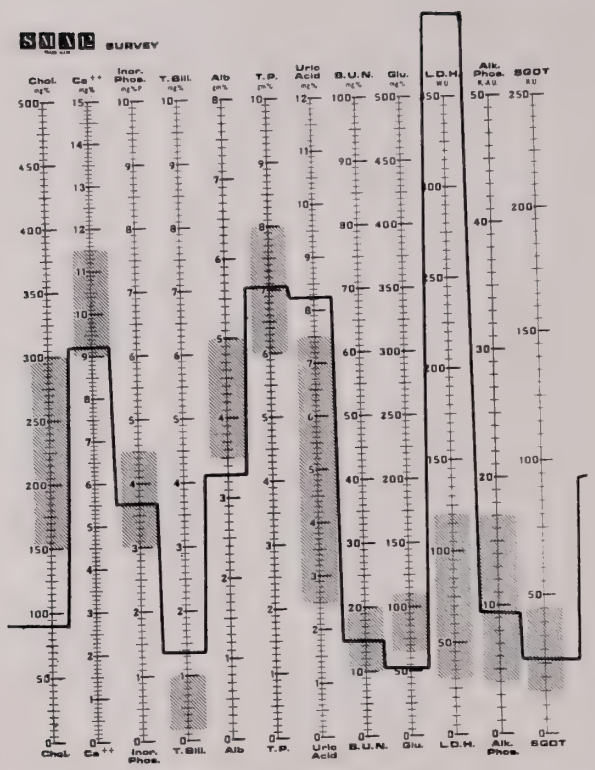


Fig. 2—An end on view of a survey model Sequential Multiple Autoanalyzer.



Pernicious Anemia Pattern

Fig. 3—Chemistry graph pattern from 68-year-old man with a macrocytic anemia with a hemoglobin of 3 Gm %. He had a megaloblastic marrow and responded to B_{12}.

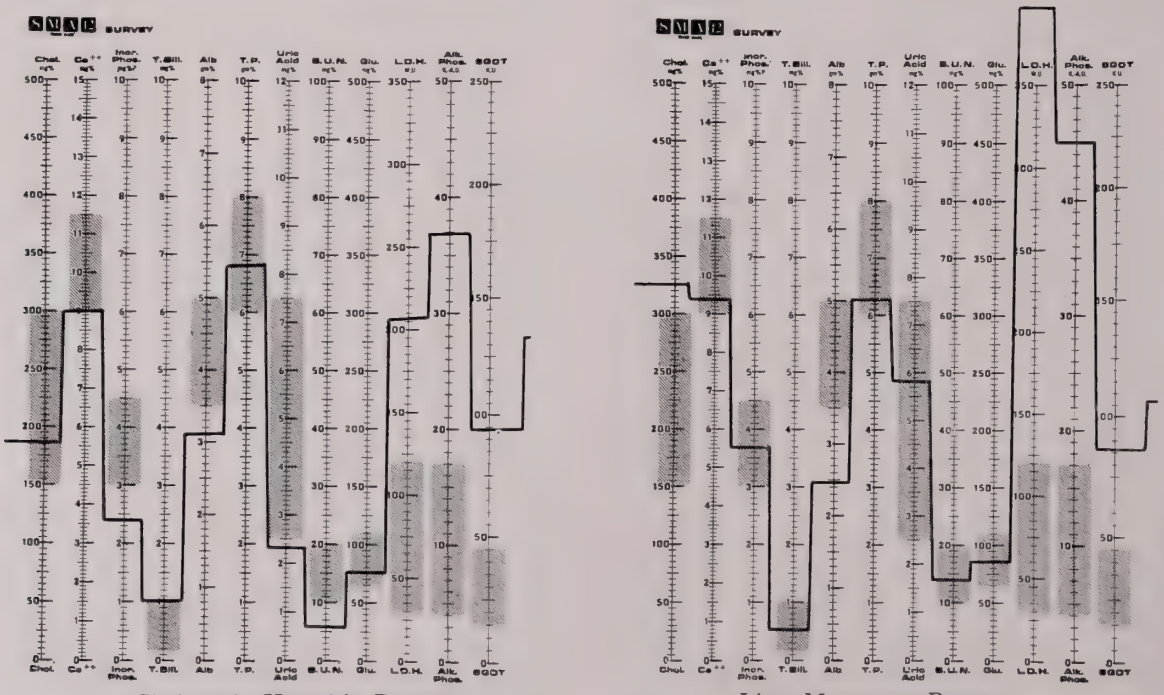
bilirubins and one third had high transaminases.

When blood hemolyzes, red cells, rich in lactic dehydrogenase, discharge their contents into the serum. If hemolysis visibly tints a serum, we so indicate on the graph and tell physicians to disregard the lactic dehydrogenase value.

Liver Disease

As a measure of liver function, serum survey chemistry graphs excel. Why? Because they provide seven tests—total bilirubin, albumin, total protein, alkaline phosphatase, lactic dehydrogenase, glutamic oxaloacetic transaminase, and cholesterol—that relate in some way to the liver; and they provide them at a reasonable cost in a readable form.

We have examined patterns of many types of liver disease, among them, portal cirrhosis, viral hepatitis, infectious mononucleosis with liver involvement, "lupoid" hepatitis, drug cholestasis, extrabiliary obstruction, metastatic tumor, and liver necrosis. Graphs alone will not differentiate these lesions. History counts. Physical examination counts. X-rays count.



Cholestatic Hepatitis Pattern

Liver Metastases Pattern

Fig. 4—Graph on left shows serum changes in a 29-year-old woman who had serum hepatitis after transfusion. Serum graph on the right was from a 57-year-old woman with colon cancer which had produced large nodules in the liver. When metastatic masses occupy a large part of the liver, both lactic dehydrogenase and alkaline phosphatase usually go up.

So do other blood tests. Even then a needle biopsy or exploratory laparotomy may be necessary to reach a diagnosis.

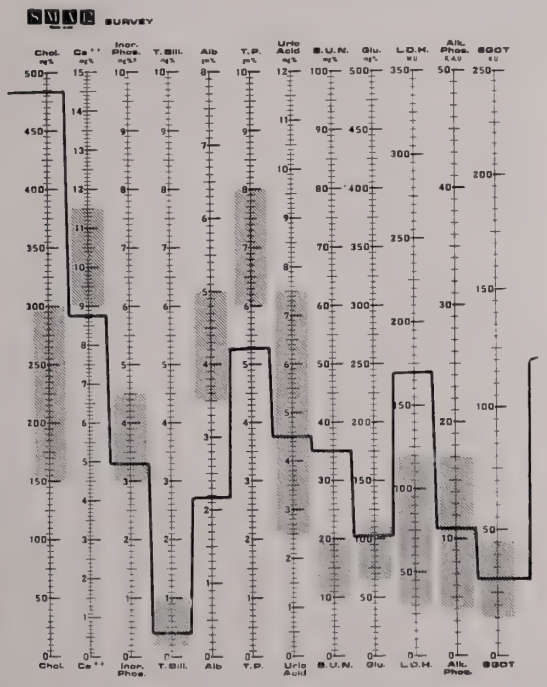
The high incidence (10.4 percent) of elevated alkaline phosphatases in our series exists partly because physicians frequently ordered the graphs to evaluate liver function. Although cholestasis from hepatitis, drugs, and tumor or stone obstruction usually produced these phosphatase elevations, we were also impressed that liver metastases could give rise to high levels and that patients with florid cirrhosis or fatty metamorphosis commonly had high alkaline phosphatases—a phenomenon observed by others.[4] The graphs in Figure 4 show two instances in which chemistry graphs helped solve diagnostic problems.

Kidney Disease

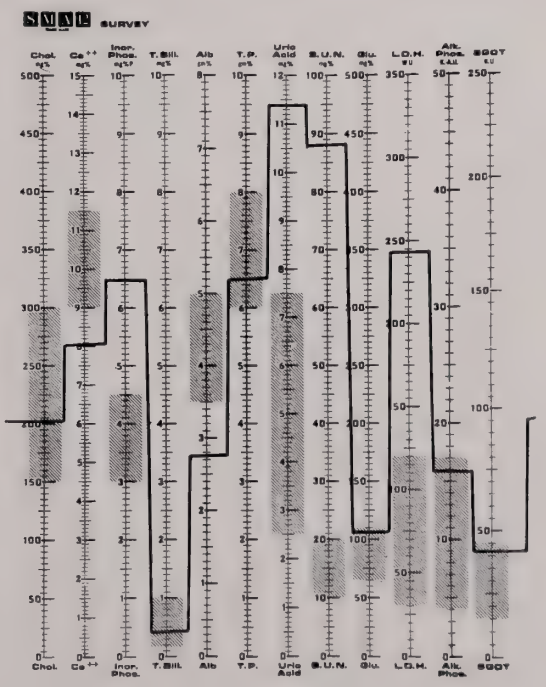
Three hundred and seventy-four or 9.2 percent of our 4000 graphs had blood urea nitrogens of greater than 25 mg%. How does this compare with other surveys? Of 2001 physicians screened at the 1966 American Medical Association Convention, six percent had blood urea nitrogens of 25 mg% or greater.[5] And of 1,080 patients tested in a practitioner's office in Columbus, Ohio, 10 percent had elevated urea nitrogens.[6]

We also observed ten urea nitrogens of 5 mg% or less. These occurred in dehydrated patients who were receiving large volumes of intravenous fluid. At Grace New Haven Hospital, Gallagher and Seligson reported blood urea nitrogens of 5 mg% or less occurring in about one percent of 16,000 tests.[7] They commented that low values in patients being infused with copious amounts of fluid implied good kidney function and a good prognosis.

In some situations, the physician with chemistry graphs can discern the nature or stage of kidney lesions. For instance, we have seen seven graphs showing severe hypoalbuminemia and hypercholesterolemia, the two serum changes that regularly occur in the nephrotic syndrome. Also we have observed 15 chronic renal failure patterns. These patients' sera showed an increased blood urea nitrogen (average 87 mg%), high phosphorus levels (average 6.0 mg%), hypoalbuminemia (average 2.8 mg%), hypocalcemia (average 8.6 mg%), low normal total protein (average 6.2



Nephrotic Syndrome Pattern



Chronic Renal Failure Pattern

Fig. 5—The patient whose serum patterns appear on the left was 40 years old, had a recent bout of glomerulonephritis, and was spilling 4.1 grams of protein a day in his urine. On the right, the patient from whom this was drawn had chronic glomerulonephritis. He died a few days later and also showed a myocardial infarction about ten days old.

mg%), and hyperuricemia (average 10.4 mg%).

Late in renal insufficiency serum phosphorus increases, because phosphate clearance decreases. The mechanism of hyperuricemia is not as clear, but according to investigators at Columbia who studied 217 patients with renal hypertension, uric acid levels increase progressively as blood urea nitrogens exceed 41 mg%. Sixty-seven percent of their hypertensive patients receiving thiazides were hyperuricemic. Our data confirms that serum uric acid increases as blood urea nitrogen rises (Table 3).

TABLE 3

Blood Urea Nitrogen	Hyperuricemic > 7.6 mg%	
	Number	Percent
0-25 mg%	308-3692	8.3%
25-35 mg%	60-224	26.8%
35-45 mg%	36-42	85.6%
> 45 mg%	36-40	90.0%
	440-4000	11.0%

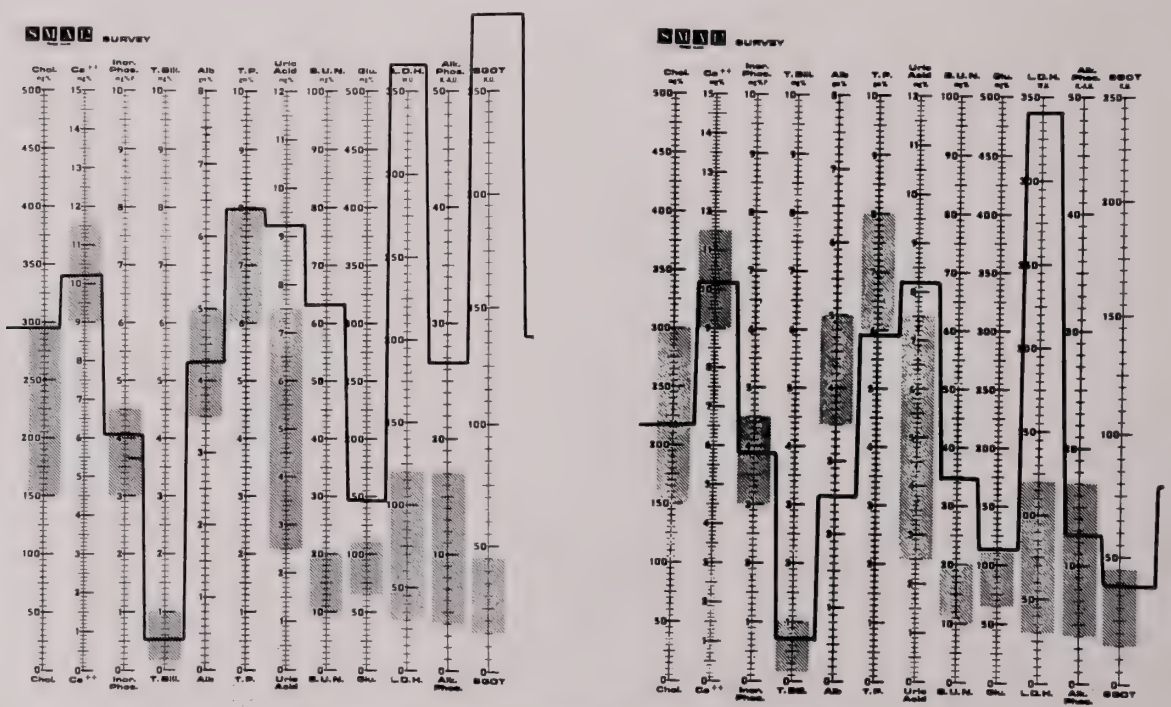
Increase in incidence of hyperuricemia among 4000 survey chemistry graphs. As blood urea nitrogen levels exceed 25 mg%, the incidence of elevated uric acid progressively rises.

Myocardial Infarction

Patients who suffer myocardial infarctions have high serum glutamic oxaloacetic transaminases and lactic dehydrogenases. Physicians, of course, know this. But they sometimes do not appreciate how quickly these enzymes rise and how long they remain elevated. Transaminase goes up six to 12 hours after chest pain starts, peaks at 24 hours, and usually drops to normal in four to five days. Lactic dehydrogenase may not rise for twelve hours, reaches its peak at two to three days, and may not descend to normal for 10 days to two weeks. By using two enzyme tests, physicians can better gauge when infarction occurred, how extensive it is, and whether it is progressing (Figure 6). Also graphs may show if the patient is hypercholesterolemic, diabetic, uremic, or if he has a congested liver with abnormal function tests. This information may help the doctor to assess the patient's prognosis and manage him later.

Hypercalcemic States

With serum surveys, physicians can sort out



Patterns of Acute and Recent Myocardial Infarctions

Fig. 6—Graph on left is from a 70-year-old diabetic male with azotemia (note uric acid elevation) whose heart had infarcted 20 hours before. Graph on right is from a 51-year-old man with known gout who had suffered infarction eight days before. His transaminase had returned to normal on the fifth day.

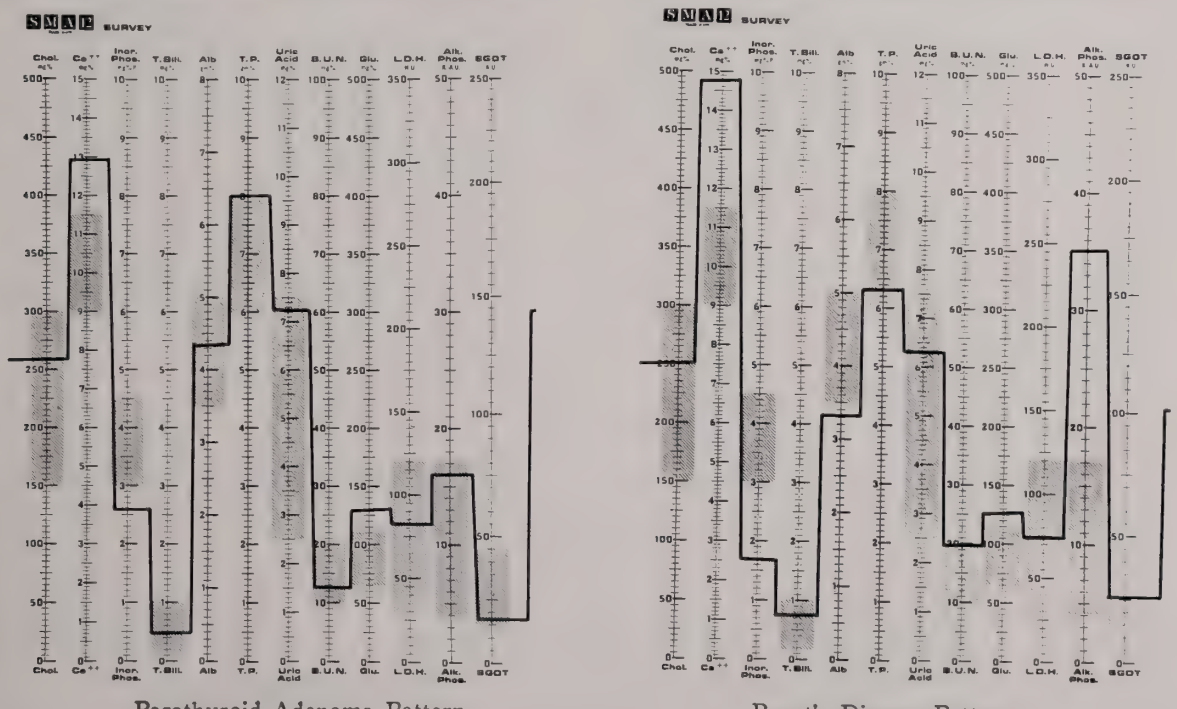
those patients with hypercalcemia and, in a few cases, track down the cause. High serum calciums occur in many diseases, but other tests on the graph—phosphorus, alkaline phosphatase, blood urea nitrogen, and total protein—will usually help to limit the differential diagnosis to a few possibilities.

Foremost among diseases causing hypercalcemia is hyperparathyroidism—a curable condition which usually results in a low serum phosphorus. In our 4000 graphs we know of one patient who had a parathyroid adenoma excised because of a high calcium (12.9 mg%) and a low phosphorus (2.5 mg%) (Figure 7). About one patient in a thousand will have an adenoma. At an Indiana Medical Clinic, Drs. Boonstra and Jackson screened with an autoanalyzer the sera of 25,847 patients.[9] As a result of high calciums that the autoanalyzer detected, surgeons excised adenomas from 26 patients.

Of what help are the alkaline phosphatase, urea nitrogen, and total protein? In older patients with hypercalcemia, high alkaline phosphatases may mean Paget's disease, metastatic tumor, myeloma, or a malignant tumor which secretes a parathyroid hormone-like substance. Also it may signal the presence of vitamin D intoxication, a sarcoid, or a fracture. Before I leave alkaline phosphatase, a word of caution about interpreting the test in the young. Children, especially rapidly growing adolescents, normally have elevated alkaline phosphatases, sometimes up to 50 King-Armstrong units.

What about high blood urea nitrogens with hypercalcemia? If high serum calcium levels persist in a patient, they affect kidney function. Sustained hypercalcemia decreases the glomerular filtration rate, interferes with renal concentration, leads to urinary calculi, and may culminate in renal failure. We have seen only two graphs with calciums exceeding 15.0 mg%. In both ureas nitrogens were greater than 100 mg%, phosphoruses were over 7.0 mg%, and uric acids exceeded 10 mg%.

What does the total protein level mean to the clinician when his patient has hypercalcemia? First, if the protein is up, it may tip him off that the patient has diseases such as multiple myeloma, sarcoid, or lymphoma. Rarely Addison's disease or hypercalcemia of



Parathyroid Adenoma Pattern

Paget's Disease Pattern

Fig. 7—Left graph is from a 60-year-old man with a history of repeated kidney stones and mental depression. After the graph disclosed this pattern, he had a parathyroid adenoma excised. Graph on right is that of an 83-year-old woman with Paget's disease. Serum calcium rarely goes up in Paget's disease unless a patient is immobilized, but the alkaline phosphatase is invariably high if Paget's involves a significant fraction of the skeleton.

infancy will have associated high serum protein levels. Second, with a total protein determination physicians can better judge the significance of calcium levels. One gram of protein (either albumin or globulin) binds about 0.8 mg. of calcium.[12] When the total protein decreases, so does the calcium. For example, a patient who has a calcium of 10.2 mg% and a total protein of 5.0 mg%, is probably hypercalcemic.

Concluding Remarks

I have discussed how chemistry graphs can assist physicians in differential diagnosis. Because I wished to be brief, I did not deal with diabetes mellitus, gout, or hypercholesterolemia. But physicians may wish to screen for all three since they may forewarn of arteriosclerosis and its consequences.[10,11] Nor did I dwell upon patterns produced by endocrine diseases, malignancies, collagen diseases, myeloproliferate disorders, or inflammatory conditions—although all may produce recognizable patterns.

Finally, I have not mentioned two important problems of multiple channel analysis—specimen control and quality control. I will emphasize them now. As in manual tests, hemolyzed, lipemic, dysproteinemic, and old sera, or specimens from nonfasting patients, can mislead the physician. After a patient has eaten, glucose levels may rise and phosphorus levels tend to decline. Also if a patient has lipemia after a fatty meal, serum turbidity interferes with colorimetric readings and can give multiple spurious results. When this occurs, we notify the physician and tell him to draw another specimen.

In nonrefrigerated specimens over 48 hours old, glycolysis rapidly takes place. Indeed, glucose values may approach zero. Moreover, glucose values drop in a few hours in sera allowed to remain in contact with the clot. Also, when sera are exposed to light, bilirubin values slowly decline. These events, of course, also affect results of manual tests done singly. The chances for their being noticed, however, are greater when 12 test results are displayed at once.

So much for specimen control. Now a comment on quality control. To standardize and control the quality of tests, we daily run commercial sera with known low, average, or high results through the analyzer. Also we use a standard after every fifth sample to assure that no electronic drift occurs, and we plot data on quality control charts after each day's run. These approaches have proved satisfactory.

Summary

I have reviewed the experience of a referral laboratory with 4000 serum survey chemistry graphs. On these graphs, twelve channel autoanalyzers record the concentrations of cholesterol, calcium, phosphorus, albumin, total protein, bilirubin, uric acid, urea nitrogen, glucose, lactic dehydrogenase, glutamic oxaloacetic transaminase, and alkaline phosphatase. Of the 4000 graphs, 1896 or 47.4 percent showed at least one abnormal test. Tests most frequently abnormal included uric acid (11.0 percent), glucose (10.5 percent), alkaline phosphatase (10.4 percent), urea nitrogen (9.2 percent), and lactic dehydrogenase (8.9 percent). Chemistry graphs can help physicians to detect and assess pernicious anemia, liver disease, renal insufficiency, myocardial infarction, pulmonary embolism, diabetes mellitus, gout, hypercholesterolemia, malignancies, and other conditions.

Acknowledgment

I thank Miss Diane McKee for gathering the data and Mr. Robert Cooper and Dr. Wayne Chadbourn for reading the manuscript.

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3. Amador, E., and Potchen, E.J.: Serum Lactic Dehydrogenase Activity and Radioactive Scanning in the Diagnosis of Pulmonary Embolism. Ann Intern Med 65:1247, 1966.

4-12 May be secured from the author or the reprints.

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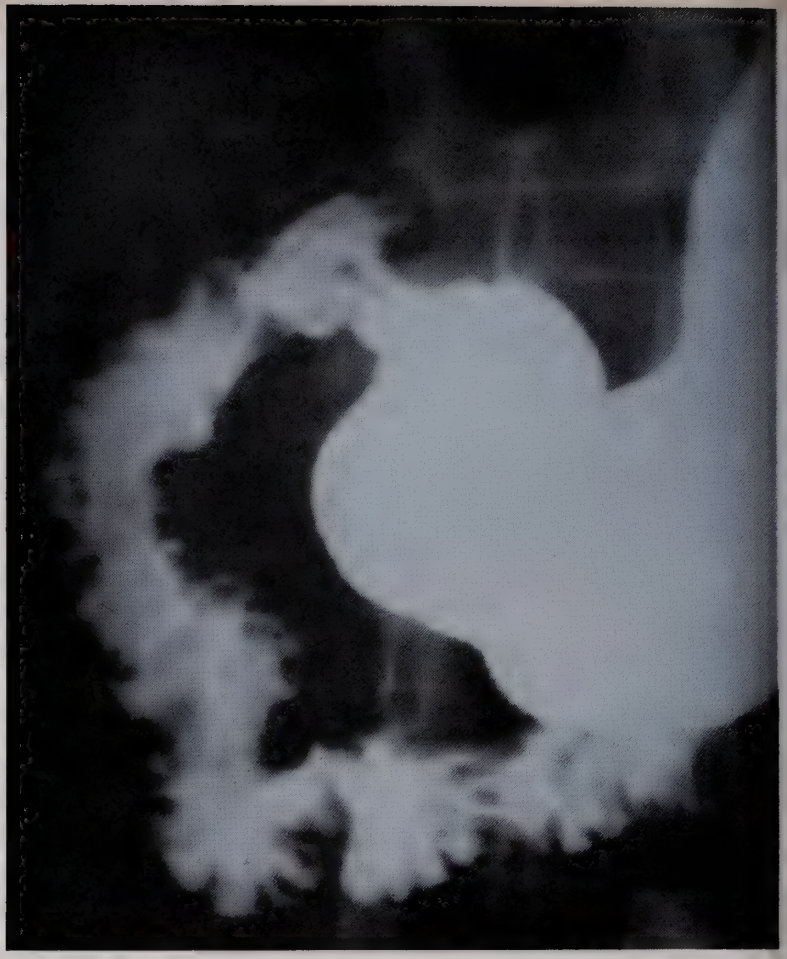
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(1) Bilbao, M. K.; Frische, L. H.; Rösch, J., and Dotter, C. T.: Hypotonic Duodenography, Scientific Exhibit, Radiological Society of North America, Chicago, Nov. 27—Dec. 2, 1966.

(2) Bilbao, M. K.; Frische, L. H.; Dotter, C. T., and Rösch, J.: Hypotonic Duodenography, Radiology *89*:438-443 (Sept.) 1967.

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Editorials

Artificial Heart

A RESEARCH and development program supported by public funds and directed by Dr. Frank Hastings of NHI is part of an international effort to develop an artificial heart. The hoped-for outcome would include improvements in the perfusion pumps employed during open heart surgery and in assist devices to relieve an overburdened or damaged heart, as well as a pump to replace the heart altogether. The research which is being conducted in commercial, university and government laboratories covers such things as basic research on pulsatile and non-pulsatile flow in living vessels, the microscopic behavior of blood particles in flow, the response of blood and tissue to foreign materials and unusual processes, biological and/or implantable energy sources and control systems for maintaining a balanced perfusion. It also includes the designing and testing of actual pumping devices.

Many goals of the artificial heart program appear within the capabilities of modern technology. The response of the living animal, however, and in particular the response of blood to prolonged exposure to foreign materials and unusual processes is not now known. Success of the artificial heart program therefore depends strongly on efforts to find materials and processes that keep blood trauma within tolerable limits.

At present hemolysis and platelet excitation are studied as a means of measuring the acceptability of a material or process in an artificial organ. An example of the kind of tolerances permitted in the former can be gained from the work of Dr. Eugene Bernstein and his colleagues in the Department of Surgery, University of Minnesota. Dr. Bernstein finds that if the imposed trauma causes sufficient intra-vascular hemolysis to cut the life spans of the red cells in half, his experimental animals succumb from renal blockages. This gives a threshold of tolerable pump-induced trauma of 0.1 mg. hemoglobin released into the plasma per 100 cc. of blood pumped by the heart. Some of the hemolysis caused by the pump occurs immediately within the pump; some occurs later as a consequence of pumping. There is evidence that a large number of pumps presently available can produce an index of hemolysis below the above threshold if only the immediate hemolysis is considered. However, experimental animals undergoing prolonged perfusions with these pumps succumb to the cumulative effect of delayed hemolysis. Additional work is required in order to find the causes and suggest cures for the delayed effect.

There is a correlation in the in-vitro tests between immediate hemolysis and auto-hemolysis during sterile incubation at 37° C. It is presently believed therefore that a pump producing a low index of immediate hemolysis will produce a correspondingly low delayed hemolysis. Thus the research on immediate hemolysis can be used to obtain an idea of the



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1. Crunden, A. B., Jr., and Davis, W. A.: Am. J. Obst. & Gynec. *65*:311 (Feb.) 1953.

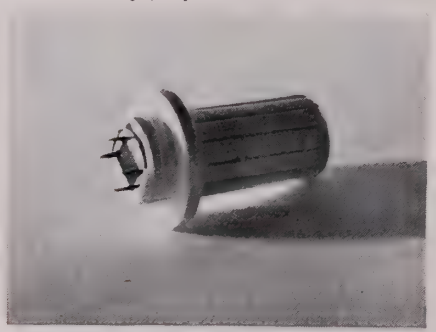


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probable cause of delayed destruction of red cells. Current work in the mechanical engineering laboratories at the University of Minnesota in cooperation with Dr. Bernstein show that if care is taken to avoid bubble formation, the flow processes in an artificial heart can be absolved of contributing to immediate hemolysis. In other words, turbulence, shear, and pressure fluctuations, in the absence of foreign surfaces, do not contribute to immediate hemolysis until very high velocities (2000 cm/sec.) are reached. In tests on different materials it is found that siliconizing the material can temporarily reduce and in some cases eliminate immediate hemolysis. It is believed that hemolysis in artificial organs occurs primarily due to interactions between blood and foreign surfaces. Similar conclusions have been reached in regard to platelet excitation. It would seem, then, that research on materials and the way flowing blood reacts with them physically and chemically holds the key to future successes in the development of artificial internal organs.

In the January and February issues of MINNESOTA MEDICINE there is a paper by Rafferty, Kletschka et al.* on a pump suitable for meeting some of the requirements of the artificial heart. The idea of a viscous flow impeller is an interesting one and should minimize damage to cells remote from the walls. The impeller shown in Figure 5 of Rafferty's paper was patented by N. Tesla in 1913. Its application as a heart replacement was first suggested in a paper by F. Dorman in 1965. The paper by Rafferty, Kletschka et al. illustrates several points worth stressing. If steady flow can be tolerated, an assortment of extremely simple, durable, and efficient pumps, with a range of flow rate-pressure head characteristics, can be designed employing conventional fluid mechanics design techniques.

In designing any pump the fluid properties must be considered. For the fluid properties of blood to give the desired pressure-flow relationships, consideration need be given only to the blood's viscosity (approximately four times that of water at pump conditions) and density. However, in the design of the equipment to minimize hemolysis (or clot formation) the minimum number of red cell wall encounters should occur, but there is not yet enough known to instruct the designer how to do this. The Rafferty team was able to keep hemolysis low by siliconizing the surfaces, but experience shows that this is only a temporary measure, as the siliconized surface elutes and hemolysis increases with time. If a stable non-traumatic surface can be developed, the pumps described will clearly be interesting candidates for future experiment and perhaps ultimate clinical use.

A final point should be made regarding the turbine pump. Although the appearance bears no resemblance to the natural heart and although its flow and pressure output is steady, instead of pulsatile, it is thought by some to be capable of accomplishing the function of the heart—that of maintaining adequate perfusion.

This leads to speculation on how other desirable functions might be attained by organs that do not resemble natural organs or, indeed, by organs that have no natural counterparts.

In this, the infancy of artificial internal organs, the artificial heart appears almost within reach. When the fundamental nature of blood-foreign material interactions is finally understood and controlled, the prospects for improving the physical well-being of man will be very exciting indeed.

Perry L. Blackshear, Jr.**
Minneapolis, Minnesota

*See Minnesota Med 51:11 and 51:191, 1968.
**Professor, Mechanical Engineering Department, University of Minnesota.

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Sensori-neural Hearing Loss

DR. WALSH* has discussed the more general causes of the serious and common medical problem, sensori-neural hearing impairment. There are many instances of this type of hearing loss in which the cause is still unknown. Recent advances in the surgical treatment of conductive hearing impairment have been dramatic but, unfortunately, in a small number of patients undergoing this type of surgery a complete sensori-neural hearing loss develops for which there is no treatment. The most common reconstructive operation, stapedectomy for otosclerosis, carries a 1 to 2.5% risk of profound sensori-neural hearing loss.[1] The risk is not great in comparison with the high percentage of patients whose hearing is restored to a socially adequate level, but when the complication does occur it is tragic. If one considers that thousands of patients have had reconstructive ear surgery for conductive hearing impairment and that thousands will have such operations in the future, it can be anticipated that there will be a formidable number of patients with iatrogenic sensori-neural hearing loss. The incidence of sensori-neural hearing impairment following stapedectomy can be reduced[1] by the selection of patients for surgery who have not previously had stapes operations or other problems that increase the risk of cochlear injury; by careful sterile technique and appropriate prophylactic administration of antibiotics; by the selection of the safest stapes replacement prosthesis; and by having the surgery performed by an experienced otologist.

Most of our attention in the last 15 years has been focused on the surgical treatment of conductive hearing loss. Although advances in the management of sensori-neural hearing impairment have been slight, nevertheless some progress has been made.

Investigation and Education

Through the efforts of such organizations as the Deafness Research Foundation, the John Tracy Clinic, and the Pre-School Medical Survey of Vision and Hearing, both the medical profession and the public are being informed of the problem of deafness and what can be done for those afflicted. Through the establishment of temporal bone banks throughout the country and the support of otologic research, knowledge is being accumulated regarding the cause, prevention, and treatment of sensori-neural hearing impairment.

Prevention

Excellent prenatal, perinatal, and neonatal care is the first step in the prevention of sensori-neural hearing loss. Care should be taken to see that the mother is not exposed to rubella or any other viral infection during pregnancy. The pregnant woman should not be given potentially harmful drugs. Rh incompatibilities that can lead to erythroblastosis fetalis should receive the utmost attention, and anoxia of the infant at birth should be avoided. The infant should receive a proper program of immunization, and all ear infections should be treated immediately and aggressively.

The recognition of potentially ototoxic drugs and the avoidance of their use is important in all age groups. I have seen patients who have received ototoxic antibiotics for relatively minor infections, with a resultant severe sensori-neural hearing loss, when a less toxic antibiotic would have been just as effective. There are, of course, life-threatening infections for which an ototoxic antibiotic is the only satisfactory treatment; but, before such an antibiotic is used, objective evidence justifying the treatment should be obtained by identifying the organism and by performing careful antibiotic sensitivity studies.

Some inner ears are more susceptible than others to injury from loud noise, but all ears are injured by excessively loud noise. The obvious solution is to control the ambient** noise or protect the patient against sound. It is much more difficult to control environmental noise than to protect the patient from noise. Some-

*Walsh, T. E.: Sensori-neural Hearing Loss: Its Nature and Etiology. Minnesota Med 50:869, 1967.

**See Test Your Word Score Page 375.

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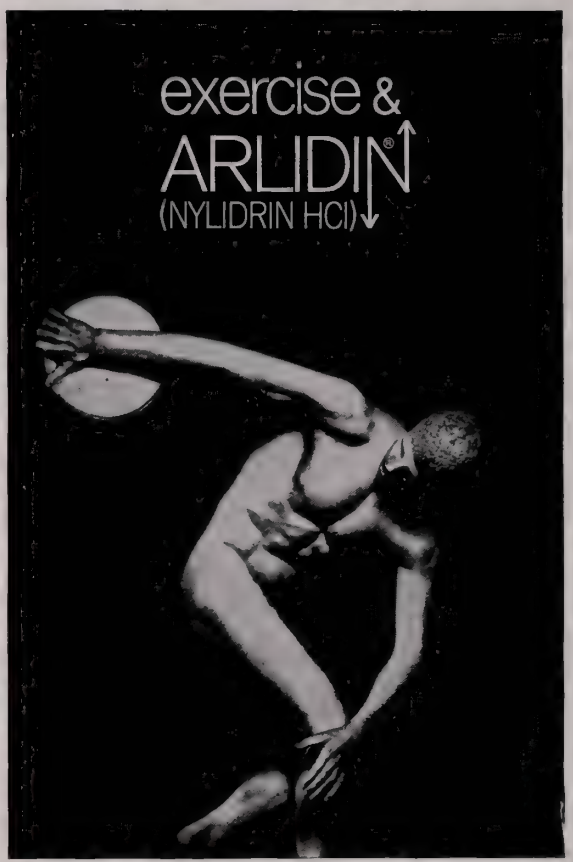
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times this is such a serious problem that it requires a change in occupation for the patient. A common cause of progressive high-tone sensori-neural hearing loss in farmers in the midwest is long exposure to tractor noise. Tightly fitting ear plugs or ear muffs will protect against this ever-present problem. Once hearing impairment has begun as a result of exposure to excessive noise, ear defenders will help to prevent further loss.

A large number of head injuries resulting in hearing impairment occur in automobile accidents. Safety belts and other safety measures will definitely help to prevent deafness.

Medical and Surgical Treatment

Once a sensori-neural hearing impairment has occurred, only in rare incidences can the condition be alleviated by medical or surgical measures. There is some evidence that the rapidly progressive sensori-neural hearing loss that occurs in Cogan's syndrome,[2] collagen diseases,[3] and latent labyrinthitis as a result of congenital syphilis[4] can be stabilized and sometimes reversed by corticosteroid therapy when instituted early enough. Sensori-neural hearing impairment in adults due to hypothyroidism can often be reversed by use of thyroid extract.[5] There is also evidence suggesting that patients with a sudden sensori-neural hearing loss due to vascular embarrassment of the inner ear can be benefited if anticoagulant therapy is begun immediately.[6] In our hands, medical therapy has been disappointing in the treatment of sensori-neural hearing loss resulting from Meniere's disease. With or without medical therapy, there is usually a progressive deterioration in hearing, although initially the hearing loss does tend to fluctuate in severity. This is particularly alarming when one considers that both ears are involved in approximately 10% of the patients with this disease. Recent studies have revealed that surgical decompression of the labyrinth[7-9] offers hope of arresting progression of the hearing loss and improvement in the hearing in patients who are operated on early in the course of the disease.

When very small acoustic neuromas are identified, it is possible in a few cases to remove the tumor through a middle fossa approach to the internal auditory meatus while preserving useful cochlear function.

Rehabilitation

Once a permanent sensori-neural hearing loss has been established, rehabilitative measures must be instituted. Until recently, it has been the rule rather than the exception to first recognize that a child is hard of hearing when he is two years of age or older. Unfortunately, precious time in learning to communicate has been lost by then. With the introduction of auditory screening of the newborn[10] by a relatively simple test to identify tentatively those infants with significant hearing impairment and the development of cortical audiometry[11] which can accurately establish auditory threshold in the infant, it is now frequently possible to diagnose a serious hearing problem in the first few months of life. When residual cochlear function is demonstrated, the infant can be fitted with a hearing aid so that he will experience the sounds of his environment. Rehabilitation also involves extensive education of both the patient and his family and, when necessary, instruction in sign language and speech-reading. In addition, the child should be given special schooling preferably no later than the age of three years. The older child and adult will also benefit from these rehabilitative measures.

At this stage of our knowledge, means of managing sensori-neural hearing loss are extremely limited. We do know, however, that, depending on the circumstances, once a sensori-neural hearing impairment is evident, the earliest possible institution of preventive, therapeutic, and rehabilitative measures offers the patient the greatest chance of significant benefit.

D. Thane Cody, M.D.
Rochester, Minnesota

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3-11 May be secured from the author.



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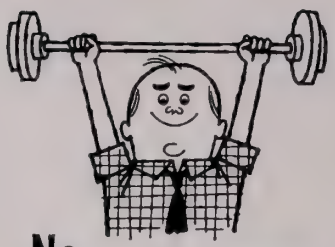
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Advantages and Limitations of a Hearing Aid

In presenting the advantages and limitations of a hearing aid, Dr. Carhart* has dealt simply and concisely with a rather complex subject. The question of whether or not to recommend a hearing aid is often diffcult to answer with confidence. The problem can be made somewhat easier and the answer more valid if one recognizes and applies the principles of hearing and amplification of sound along with a thoughtful evaluation of the patient as suggested in this article.

The discussion of the limitations of a hearing aid is particularly pertinent at a time when we are prone to think that the wonders of electronics can or should overcome all obstacles, including deafness. This simply is not the case at present, and there is no prospect of early developments that will surmount the major difficulties that Dr. Carhart mentions.

In evaluating the developments and changes in hearing aids over the past decade, we are faced with the indisputable fact that most of the improvements made have been in terms of size and convenience rather than in performance. It appears to be impossible at present to build the best quality amplifiers for most hard-of-hearing listeners in the tiny cases that are popular in current hearing aids. This frequently raises the question of what compromises should be made among performance, convenience, appearance, and cost. Because usually no single instrument can be proved superior for a specific person under all circumstances, the selection of a hearing aid is generally acknowledged to be a reasonable balance between objective tests of performance and a number of judgments on practical and personal aspects of the problem.

It usually is advisable, if not actually crucial, that a person considering a hearing aid for the first time have professional help in selecting a suitable instrument and in learning to use it optimally. Such help is becoming available to more and more people through the expansion of clinical and educational services in audiology. Most otolaryngologists and many other physicians either are active in providing and promoting such services or at least know where to refer patients for this kind of help. It is to be hoped that all physicians will share this knowledge and will practice appropriate referrals of patients seeking help with regard to hearing aids.

LeRoy D. Hedgecock, Ph.D.
Rochester, Minnesota

*Carhart, R.: The Advantages and Limitations of a Hearing Aid. Minnesota Med 50:823, 1967.

Effective Use of Serum Creatine Phosphokinase Assay*

The serum creatine phosphokinase assay was introduced into clinical medicine in 1959 by Ebashi and co-workers, who observed high activity of the enzyme in sera of patients with progressive muscular dystrophy. The current status and limitations of the serum creatine phosphokinase test and the possible significance of abnormal values are discussed in a recent review by Loegering and co-workers.[1] Since the enzyme is stored in high concentrations only in nerve tissue and skeletal and cardiac muscle, increase in serum creatine phosphokinase activity usually indicates enzyme release from one of these tissues as a result of destruction or excessive permeability of cells in these tissues; in-vivo or in-vitro hemolysis, hepatic disease, or pulmonary infarction does not result in high serum creatine phosphokinase levels.

Effective use of the creatine phosphokinase test requires a number of precautions. The normal range of values for the type of assay used by the laboratory must be known for adults and for infants of each sex. The reproducibility and sensitivity of the test are increased if –SH protecting agents, such as cysteine or glutathione, are added to the reaction mixture.[2,3] Unexpected high values may be observed in the recovery phase of diabetic acidosis, in chronic alcoholics after a binge, in the puerperium, and after prolonged and

*Loegering, D. J., Critz, J. B., and Wagner, J. A.: Serum Creatine Phosphokinase as a Diagnostic Aid: A Review. Minnesota Med 50: 1751, 1967.

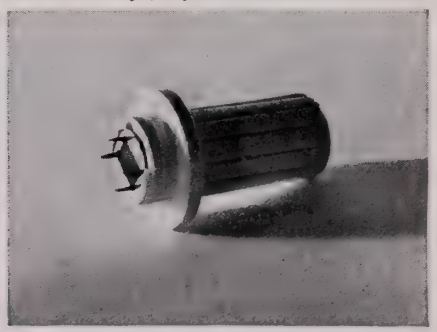
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heavy physical exertion.[3,4] Finally, high serum creatine phosphokinase levels may be observed in myxedema even when other clinical evidence of a myopathy is lacking; conversely, creatine phosphokinase levels are usually not increased in hyperthyroidism even when the condition is complicated by myopathy.[2]

The serum creatine phosphokinase levels are increased in 79% of the definite carriers of the Duchenne type of muscular dystrophy and in approximately half of the probable or possible carriers of this disease.[5] High levels are encountered in patients with the Duchenne type of muscular dystrophy early in the course of the disease, and the serum levels decrease as the disease advances, possibly due to reduction in total muscle mass. In other types of dystrophies the increases are less marked and less constant. A normal serum creatine phosphokinase level in a child who has shown clinical and electromyographic evidence of myopathy since birth suggests a congenital myopathy other than dystrophy, such as central core disease, nemaline (Z-disk or rod) myopathy, megaconial myopathy, or myotubular myopathy. In those rare cases of late-onset nemaline myopathy observed to date, the serum creatine phosphokinase levels were not increased.[6]

In inflammatory myopathies associated with acute destruction of muscle fibers there frequently is a pronounced increase of the serum creatine phosphokinase level. In these cases the decreasing levels of the enzyme may serve as a guide to the efficacy of corticosteroid hormone therapy, although improvement in muscle strength may not appear for several weeks after the serum creatine phosphokinase levels have started to decrease. In weakness induced by excessive corticosteroid hormone therapy, the creatine phosphokinase levels are usually not increased. In acute myocardial infarction or in myocardiopathies due to other causes, serum creatine phosphokinase and glutamic-oxaloacetic transaminase levels are both increased. However, the creatine phosphokinase values represent a more reliable index of myocardial damage because they are unaffected by passive congestion of the liver or by other types of hepatic disease that might coexist. It thus appears that, when carefully used, the creatine phosphokinase test represents a valuable and important diagnostic measure in clinical medicine.

Andrew G. Engel, M.D.
Rochester, Minnesota

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Drug Therapy for Treatment of the Manic State*

THE HERALDING of a relatively new drug for the treatment of the manic state is noteworthy and long awaited. Probably no disease causes more pain, misery, despair, sadness, or torture to self and others than depression. It probably is the most frequently encountered, yet often least recognized, illness in the diagnostic domain of medicine.

Those who ply their trade in the nuances of mental illness know full well the frustration of

*Brauer, William: Use of Lithium Carbonate in Private Psychiatric Practice. Minnesota Med 51:109, 1968.

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coping with the "manic" patient. His ability to deceive others and deny to himself the prodromal symptoms of his illness is of historic significance. Any new approach offered to treat the fulminating symptoms of mania is gratefully appreciated. Least of all it places an aggressive tool into the hands of the psychiatrist. Too often his role has been identified as passive and nonresponsive by himself and others, with neither party realizing that such a position is untenable in the "life game." A psychiatrist should be a good listener, but to listen well requires alertness, "savvy," and a comprehension of the unconscious; and such skills are not passively acquired. Mental activity implies motion, energy, and involvement. The acquisition of new drugs for the treatment of mental disorders will be acknowledged in the future more for their relatedness to etiology than for specific results in treatment, even if promising or successful, or both.

Richard M. Steinhilber, M.D.
Rochester, Minnesota

Test Your Word Score

Ureterolithotomy—*operation for stone in ureter* (page 339).

Prodigious—*monstrous* (page 343).

Cylindroma—*a tumor in which the stroma has the form of elongated, twisted cords of hyaline material* (page 347).

Gaussian—*pertaining to Karl F. Gauss, German mathematician* (1777-1855) (page 352).

Ambient—*encompassing* (page 367).

Schistosomiasis—*infestation with Schistosoma, a species of blood fluke* (page 379).

You May Be Right

While in Madagascar this past summer, working at the Manambaro Lutheran Hospital, I found schistosomiasis* to be a very common disease. To establish the diagnosis it is common to take a punch biopsy of the rectal valves. Frequently this led to severe rectal bleeding, difficult to control. Poor clotting mechanism was encountered occasionally, especially in patients with advanced liver damage. Cooperation of the patient wasn't always the best, and transfusions were sometimes difficult to do because of the lack of donors.

To circumvent this and still get an adequate biopsy I used an ordinary ring clamp with horizontal grooved edges. Using this instrument, it was possible to seize the rectal valve through an anoscope and close the clamp tightly, which then made it possible to remove a portion of mucosa caught in the jaws of the instrument. An adequate biopsy for examination without hemorrhage was readily obtained in this manner. I recommend this biopsy procedure for schistosoma ova, rather than the use of a punch-biopsy instrument.

Lloyd H. Klefstad, M.D.
Greenbush, Minnesota

*See Test Your Word Score Above.

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The Editor's Soliloquy

Family Physician

Almost from time immemorial the doctor has been dignified as Family Physician. Occasionally and affectionately he has been dubbed "Good Old Doc" or, in a more detached and sardonic vein, as bone-setter, medico, or one of the pill compounds: pillbag, pill-pusher, pill-shooter. In his capacity as surgeon he is sometimes aptly termed sawbones, a sobriquet first appearing in the literature when Charles Dickens used it in Pickwick.

After long investiture with the familiar and acceptable title of Family Physician, latter day modern bureaucratic advocates of a more dignified and upgrading name progressively graduated him to General Practitioner, GP and Generalist; and yet more recently to the more exalted Primary Physician.

The term Generalist was obviously designed to place the doctor in the category of the other "ists" (specialists). While Generalist has the advantage of compactness and euphony it lacks specificity, unless it were preceded by Medical.

Speaking of suffixes: -ian (obstetrician) grafted on to General would yield Generalian—so uneuphonious a hybrid that it would die aborning. As for the suffix -geon (surgeon): Generalgeon would be such an etymological monstrosity that its pronunciation alone would Nicodemus it into prompt retirement and oblivion.

How about the good old Greek suffix, -path? Homopath (homo plus path) would be excellent per se but, in the minds of the undiscriminating, would surely be confused with homeopath. Then how about omnipath (omnia plus path)?

We could go on and on—getting more and more abstracted in the semantic jungle of nomenclature. Why not just settle for Family Physician: an appellation comfortable and reassuring to our patients and an honorable title that has never been debased and that requires no enhancement. Why discard it in a will-o-the-wisp search for even higher terminology status. I can think of nothing more prestigious, more endearing and more honor-conferring than to be called the Family Surgeon, the Family Internist, the Family Physician.—

Carl O. Rice, M.D.

Old Doc Hess says—The left hand hand-shaker is the type of individual who, like a swimmer doing the Australian crawl, offers his hands alternately right and left as he moves toward his chosen guest of the evening.—C.O.R.

Our Own Fault?

Varicose veins are the result of an improper selection of grandparents.—*Osler*

Something for Nothing

Sometimes one pays most for the things one gets for nothing.—*Albert Einstein*

Always arise from the table with an appetite and you will never sit down without one.—*William Penn*

Landouzy-Dejerine Syndrome

This slowly progressive muscular dystrophy, which affects mainly the muscles of the face, shoulders, and pectoral girdle, was first described by Landouzy and Dejerine in 1885. The condition appears in late childhood or in adolescence. Both sexes may be affected as the syndrome characteristically is inherited and transmitted as a Mendelian dominant.

The most common initial symptom is inability to raise the arms above the head or keep them in that position. Some patients at an early age have difficulty in completely closing the eyes. The physical signs are those resulting from weakness and atrophy of the various muscle groups involved. First affected are the large muscles of the pectoral girdle, which eventually show marked atrophy. In more advanced conditions the atrophy results in a striking flattening of the entire anterior chest. The cheekbone and the face are also severely affected. Involvement of the cervical muscles is usually moderate, and there is atrophy in the suprascapularis and infrascapularis. A later development is atrophy of the erector spinae group of muscles and involvement of the deep muscles of the pelvis, producing an exaggerated lordosis with a waddling, rather grotesque gait. This peculiar walk is seldom associated with other conditions.

The course of this muscular dystrophy is usually benign. There may be long periods of remissions; and in some cases for reasons not known, the condition may eventually cease to progress. Only occasionally is a patient severely handicapped before reaching old age. No specific treatment is known. Various recommended nutritional supplements are of doubtful therapeutic value.

Durham, Robert H.—Encyclopedia of Medical Syndrome
Hoeber Medical Division, Harper and Row, New York

Bio-Dynamo-Chromatic-Diagnosis and Therapy

Whenever the irregulars in the healing art assemble for the purpose of exchanging trade secrets and telling each other how good they are, George Starr White, M.D., F.S.Sc. (Lond.), D.C., Ph.D., LL.D., Los Angeles, is among those present. He developed the fancy-name system that combines a lot of hocus-pocus—it seems one diagnoses disease by a "Sympathetic Vagal Reflex." To elicit the said phenomenon, the patient faces east or west and his abdomen is thumped until a dull area is found. Then colored lights are thrown on the abdomen and the thumping is continued. A ruby and blue light with associated dullness means one thing and a green light combination another.

In 1925, White produced the last word in this fancy business, the Rithmo-Chrome and Duo-Colors. He has a lot of books to sell and a lot of apparatus. For instance, in his latest announcement, Figure 10 shows a "person sitting on a Filteray Cushion and receiving Filtered Ultrared Rays while doing Rithmo-Chrome breathing and inhaling Oxygen-Vapor or Medicated Vapor and at the same time getting therapeutic effect of the magnetic forces of the earth, as he is grounded and facing exactly north and south." If the Duo-Colors are added to this, Dr. White affirms, the patient is certainly getting "Natural Methods Condenst." And if he isn't getting that, what is he getting?*

*Morris Fishbein, M.D.: New Medical Follies, 1927.



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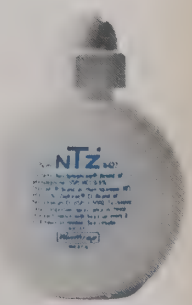
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Precautions: Limit dosage to smallest effective amount in elderly or debilitated patients (not more than 1 mg, one or two times daily initially) to preclude ataxia or oversedation, increasing gradually as needed or tolerated. As is true of all CNS-acting drugs, until correct maintenance dosage is established, advise patients against possibly hazardous procedures requiring complete mental alertness or physical coordination. Driving during therapy not recommended. In general, concurrent use with other psychotropic agents is not recommended. If such combination therapy is used, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam), such as phenothiazines, barbiturates, MAO inhibitors and other antidepressants. Advise patients against simultaneous ingestion of alcohol or other CNS depressants. Safe use in pregnancy not established. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Observe usual precautions in impaired renal or hepatic function. Periodic blood counts and liver function tests advisable in long-term use. Cease therapy gradually.

Side Effects: Side effects (usually dose-related) are fatigue, drowsiness and ataxia. Also reported: mild nausea, dizziness, blurred vision, diplopia, headache, incontinence, slurred speech, tremor and skin rash; paradoxical reactions (excitement, depression, stimulation, sleep disturbances, acute hyperexcited states, hallucinations); changes in EEG patterns during and after drug treatment. Abrupt cessation after prolonged overdosage may produce withdrawal symptoms (convulsions, tremor, abdominal and muscle cramps, vomiting, sweating) similar to those seen with barbiturates, meprobamate and chlordiazepoxide HCl.

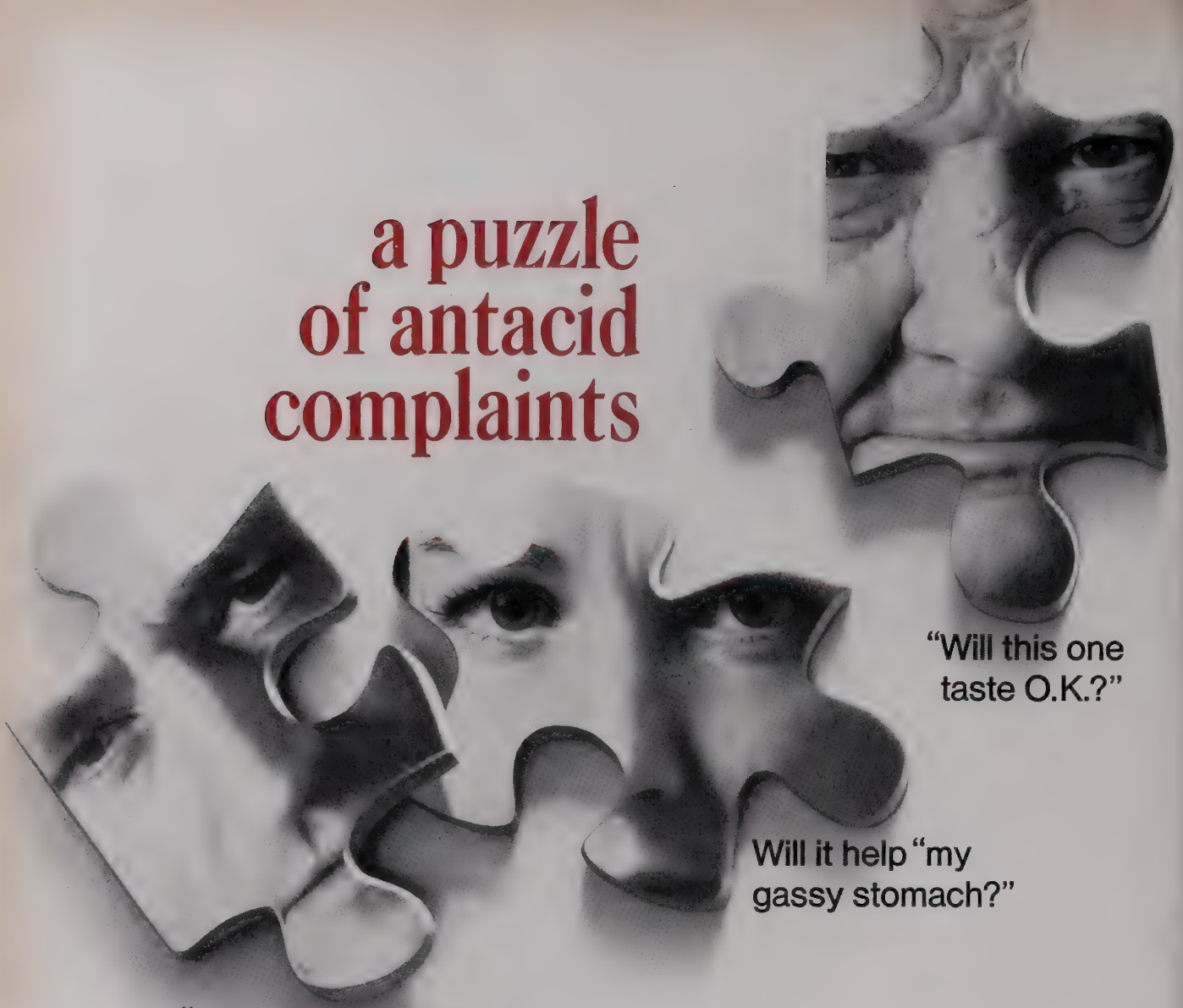
Dosage—Adults: Mild to moderate psychoneurotic reactions, 2 to 5 mg b.i.d. or t.i.d.; severe psychoneurotic reactions, 5 to 10 mg t.i.d. or q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; muscle spasm with cerebral palsy or athetosis, 2 to 10 mg t.i.d. or q.i.d.

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References: 1. Hoon, J. R.: Arch. Surg. *93*:467 (Sept.) 1966.
2. Danhof, I. E., Personal communication.

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Breathholding

QUESTION: While examining an eighteen-month-old child recently, I met with a great deal of resistance and negative behavior. The child became exceedingly angry and cried violently. Then he stopped breathing, became cyanotic, rigid, and momentarily unconscious for about one minute. Having never had such an experience, I write to inquire as to its meaning, cause, and how to deal with it.

ANSWER: This phenomenon was first described in 1848. Because of its relatively low incidence, little mention is made of it during medical school days and internship training. Clinical experience indicates that such behavior invariably is symptomatic of acute emotional distress arising from three primary sources: (1) disturbed parent-child relationships, (2) fear, or (3) pain. Age on onset is reported as being between six and eighteen months. The pattern rarely persists beyond four or five years. Unless the source of difficulty is defined and help is given, these spells often are replaced by temper tantrums or other behavioral disorders.

Since breathholding is rarely fatal, parents should be reassured to reduce their anxiety titer. Concomitantly, parental expectations of the child and their methods of managing him should be explored. If inappropriate, they should be corrected through counselling. In rare cases a period of separation —placing the child in a hospital—may be indicated.

R. A. Jensen, M.D.
Minneapolis, Minnesota

Remedies Derived From The Poplar Tree

We have already mentioned, when speaking of the unguents, the use that is made of the berries of the white poplar. A potion prepared from the bark is good for sciatica and strangury, and the juice of the leaves is taken warm for earache. So long as a person holds a sprig of poplar in his hand, there is no fear of chafing between the thighs. The black poplar is looked upon as the most efficacious. The seed of it, taken in vinegar, is good for epilepsy. The leaves, boiled in vinegar, are applied topically for gout. A moisture that exudes from the clefts of the black poplar removes warts and pimples caused by friction.—*Pliny*

A Surfeit

I die by the help of too many physicians.—*Alexander the Great*

A New Tongue

During the fierce fighting of August 1943 a wounded soldier, Pyotr Sigayev, was brought to a field hospital. His life was in no danger, but the shrapnel wound caused great concern.

His head was a gruesome sight. Half his face was mutilated beyond recognition. The lower jaw was fractured in two places. All but four of his teeth were missing. Unintelligible sounds came from his lips. Sigayev's tongue was crushed. Mere rags of tissue remained in its place, and had to be cut out to the root at once under novocain anesthesia.

The patient was evacuated to Moscow. By the time he arrived at the Central Institute of Traumatology his condition had deteriorated. The tongueless man could not talk. What was worse, he could hardly chew or swallow.

At the institute the surgeons first tackled his shattered jaw. A month later, after the patient was somewhat fortified by artificial feeding, they risked an operation: All scars and adhesions in the vicinity of the fracture were cut, the jaw pulled forward to its normal position, and put in a plaster cast for six weeks.

After the lower jaw healed artificial dentures were attached to the four remaining teeth. This facilitated chewing. The splinters of the lower jaw were removed and the bone defects made up by a transplanted cartilage. Another cartilage graft helped to shape the chin.

There now remained the tongue. The only possible thing to do was to make a new one. The most suitable material for it was the skin; but a very large piece of it was required. It was to be taken from the patient's back. A round Filatov stalk was prepared under the shoulder-blade. But the skin alone was too thin to suit the purpose. The subcutaneous tissue and a layer of fat would have to go with it. That would make the stalk thick enough.

The graft was to take the shortest possible route to its destination. Transferred from the back to the belly, it was further transplanted to the arm. The patient had only to raise his arm to bring the stalk to his mouth.

The operation was completed in November 1946. The root of the tongue was sutured with silk thread and drawn out as far as it would go. Operating in the depth of the oral cavity was extremely difficult. The surgeons removed the scars from the surface of the tongue stump. The site was then ready to receive the Filatov stalk.

The end of the stalk was unrolled and inserted into the oral cavity, where it was sewed on to the upper and lower surface of the tongue root. Now one end of the stalk was implanted in the root, and the other remained on the arm.

For three weeks Sigayev's arm remained pressed to his mouth. To hold it in that position it was bandaged to the head. Surgeons kept constant vigil over their patient. All went well. The stalk took root. It was finally cut away three inches from the root. The smaller part of it remained on the arm, and was soon removed; the second part was in the mouth, grown firmly to the root, which had retained its original muscles. That was how a new tongue was made.

In two weeks Sigayev was mute no longer. His speech was perfectly intelligible.

This delicate operation, skillfully performed by Professor Mikhelson, was another triumph of Soviet plastic surgery.*

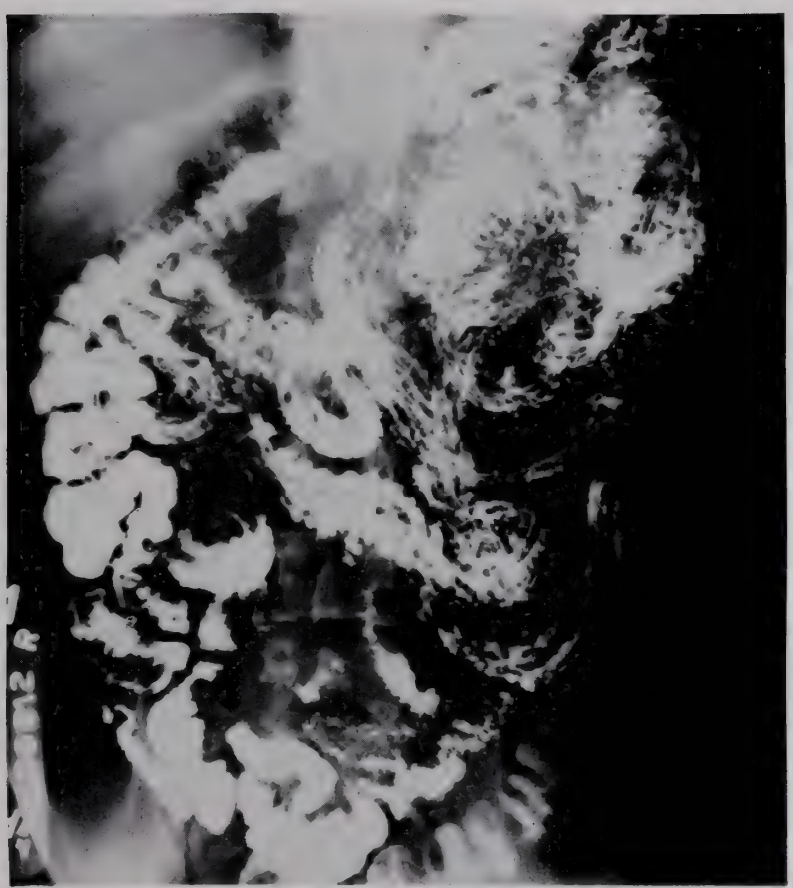
*L. Fridland, M.D.: The Achievement of Soviet Medicine, 1961 edited and translated from the Russian by W. Horsley Gantt, M.D.

The Viewing Box

Vietnam Veteran

This is a 20-year-old negro Marine corporal who was admitted with a history of abdominal pain for 24 hours. He returned from Vietnam 10 months ago and has been in good health until this rather sudden onset of pain.

What is your diagnosis? (See next page).



Diagnosis: Ascariasis of the small bowel.

Ascaris is a parasite that is widely distributed throughout the world. It is of importance especially in pediatrics, because even one worm may produce a variety of clinical manifestations.

The adult worms measure 15 to 30 cm. in length and about 3 to 5 mm. in diameter. The eggs undergo an incubation period in the soil, after which they are ingested by the patient. Once in the small intestine the larvae are hatched, then penetrate the intestinal wall and reach the lungs by way of venules or lymphatics. In the lungs they can cause a pneumonia characterized by high fever, chills, cough, and bloody sputum containing larvae. From the alveolar spaces they migrate up the respiratory passages and are swallowed. Once in the small intestine they grow into adults of both sexes. In heavy infections some of the larvae continue into the general circulation and reach various organs and tissues.

Radiologically the adult parasite appears as a longitudinal and cylindrical filling defect in the contrast-filled small bowel. They are usually found in the jejunum, but may migrate to the nasopharynx, stomach, or appendix. Large masses of worms may cause intestinal obstruction. The contrast agent may be ingested by the worms and remain visible as a fine threadlike shadow in their intestinal tract.

The diagnosis is confirmed by recovery of the parasite from the stool or sputum. The treatment today is usually with a piperazine salt, such as piperazine citrate (Antepar).

Peter Ullrich, M.D.*
Minneapolis, Minnesota

*Resident in Radiology, Veterans Administration Hospital.

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Aerotherapy

Among the hundred or more types of healing offered to the sophisticated is aerotherapy. Obviously aerotherapy means treatment by air, but in this instance hot air is particularly concerned. The patient is baked in a hot oven. Heat relieves pain and produces an increased flow of blood to the part heated. The blood aids in removing waste products and brings to the part the substances that overcome infection. There is nothing essentially wrong about hot air therapy.

Aerotherapy as one department of physical therapy becomes a cult when it is used to the exclusion of all other forms of healing. In New York a progressive quack established an institute equipped with special devices for pouring hot air over various portions of the body. He issued a beautiful brochure, illustrated with the likenesses of beautiful damsels in various states of negligee, smiling the smile of the satisfied, under his salubrious ministrations. In this document appeared incidentally the claim that hot air will cure anything from ague to zoster.*

*Morris Fishbein, M.D.: New Medical Follies, 1927.

Sources of sinus headache



REGION OF SENSATION

FRONTAL SINUS—headache localized over the frontal region, commonly beginning in the morning. Eyes painful to touch, may be slight swelling over eyes, puffy eyelids.

SPHENOID SINUS—most difficult to diagnose. Headache or sense of pressure over vertex. May be pain in ear or mastoid region.



MAXILLARY SINUS—headache and tenderness under eyes at top of cheekbones, usually starting in early afternoon. Possible swelling of cheek. Pain in jaw and back teeth.

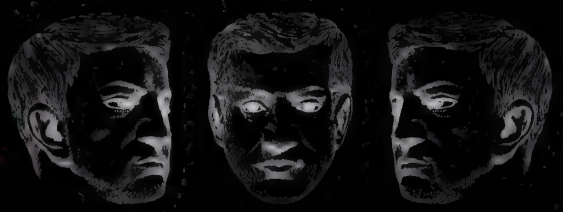
ETHMOID SINUS—headache, tightness in upper part of bridge of nose and well down its sides. Pain, deep-seated behind the eyes and in inner corners of the eyes.



TURBINATES—pain along medial and lateral walls of the inside of the nose. Headache in frontal region, along supraorbital ridge, a feeling of fullness in the head.

Source of symptomatic relief

SINUTAB



Sinus headache is often a reflection of congestion in the nasal mucosa. The pain that results in the various regions of the head may help in determining the particular structure(s) responsible. The Sinutab formula is specifically designed for symptomatic relief of sinus headache and nasal congestion. **Sinutab** *not only* **provides an effective decongestant** — to reduce mucosal engorgement and facilitate freer breathing — *and* **an antihistamine** — to help reduce edema and excessive secretions — but it *also* provides, in contrast to other leading decongestants, **two analgesics** for immediate relief of pain and discomfort.

And, too, the Sinutab dosage schedule of 2 tablets, *q.* 4 *h.* permits controlled and continuing analgesic relief.

Adverse Reactions: Epigastric distress, drowsiness, dizziness, insomnia and nervousness.

Precautions: Instruct patients not to drive or operate machinery if drowsiness occurs. Use with caution in patients with thyroid disease, heart disease, hypertension, diabetes or kidney disease. Excessive dosage or prolonged use may cause kidney damage.

Dosage: Adults—2 tablets every 4 hours.

Each tablet contains 150 mg. acetaminophen, 150 mg. phenacetin, 25 mg. phenylpropanolamine HCl, and 22 mg. phenyltoloxamine citrate.

SPECIFIC FORMULA SINUTAB® FOR SINUS HEADACHE

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Sinutab® with Codeine.* Each tablet contains 15 mg. (¼ gr.) codeine phosphate (Warning: May be habit forming), 150 mg. acetaminophen, 150 mg. phenacetin, 25 mg. phenylpropanolamine HCl, and 22 mg. phenyltoloxamine citrate.

Sinutab® Pediatric Suspension. Each 5 ml. teaspoonful contains 300 mg. acetaminophen, 12.5 mg. phenylpropanolamine HCl, and 10 mg. phenyltoloxamine citrate.

*Subject to Federal Narcotics Regulations.

For 1 complimentary bottle of 30 Sinutab tablets, write: J. S. Travis, Warner-Chilcott Laboratories, Morris Plains, N.J. 07950. Please mention this journal.

5-IN-81-4C

WC **WARNER-CHILCOTT** Morris Plains, N.J.



Tumor Conference

Esophageal Cyst

BENIGN ESOPHAGEAL lesions make up 0.5 to 2.5% of all esophageal tumors, leiomyomas being the most common. Esophageal cysts or duplications of the esophagus are considered to be rare.[11] With this in mind, we felt that the following case report of an esophageal cyst that occurred in an adult would be of interest.

Case Report

A 33-year-old white male was admitted to the Minneapolis Veterans Hospital because of an acute onset of epigastric pain that radiated around both sides and to the back. This pain had persisted for one week and was less intense following vomiting. Emesis would occur regularly, approximately fifteen minutes after meals. The patient had been examined at another hospital and given antacids, which relieved his epigastric pain.

History

Past history and systems review revealed that the patient had an active duodenal ulcer diagnosed by x-ray in 1961, which had been present by history since age 15. Diabetes mellitus had been diagnosed six years previously. At that time the patient was started on oral hypoglycemic agents but since has required 15 units NPH insulin daily. Six years ago he experienced an unexplained episode of back pain. In 1962 he swallowed an unknown amount of "stripping" acid. He did not experience vomiting or other clinical evidence of esophagitis or obstruction at that time.

Examination

Physical examination revealed a well-developed, healthy-appearing male with a blood pressure of 120/70, a regular pulse of 88, and a weight of 160 pounds.

Laboratory Studies

Laboratory findings consisted of a urinalysis that showed 1-3 wbc. with specific gravity of 1.027, albumin 0, sugar 4+, acetone slight; and a creatinine clearance 98 ml/min. Hematology—wbc. 14,000 with 75% PMNs, 17% lymphs, 8% monos, 1% eosinophils, and hemoglobin 13.3 mg%. Serology was negative. Chemistries: glucose 164, serum acetone slight, BUN 22. Gastric analysis revealed 40° total acid and 30° of free acid. Serum electrolytes were sodium 138, potassium 4.8, chloride 92, CO_2 24, calcium 10.3 and phosphorus 3.5. Prothrombin time was 13.7 seconds with a control of 12.5 seconds. BSP was 2% and alkaline phosphatase was 13.3, total protein 7.6 with an albumin of 4.1 and a globulin of 2.5. SGOT was 8. Stool guaiacs were negative.

A chest film showed a small retrocardiac density to the left of the vertebral column. An esophagram and upper gastrointestinal series showed a smooth deformity of the distal third of the esophagus. Cineradiography of the esophagus confirmed the presence of

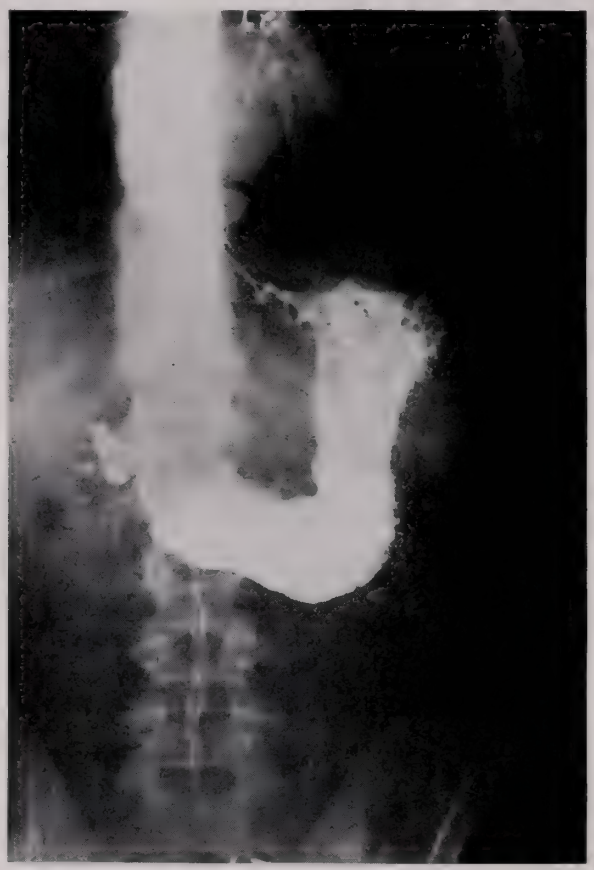


Fig. 1—Smooth deformity of the distal esophagus secondary to extraluminal compression by a retrocardiac mass. Note also the deformity of the duodenal bulb.

this deformity and showed an absence of normal peristalsis in this area.

Treatment

On March 15, 1967, the patient underwent a left thoracotomy. A cystic lesion of the lower esophagus was found, with no line of cleavage between the mass and the esophagus. The mass was opened at a point most lateral to the palpated nasogastric tube and found to be lobulated with two communicating cavities. Since no cleavage plane could be developed between the cyst and the esophagus, the mass was partially removed, leaving the common cyst-esophageal wall intact (Figure 1). The thickened mediastinum was closed loosely over the esophagus, leaving the distal part open for drainage. Microscopic examination of the specimen showed ulceration in one portion of the cyst wall. The lining of the cyst was pseudocolumnar ciliated epithelium.

The postoperative cineradiograph revealed patency of the esophagus with normal passage of barium (Figure 2). The patient has gained weight postoperatively and has no dysphagia.

Discussion

Blasius is given credit for having been the first to report a case of esophageal duplication in 1711.[12] The area of greatest controversy concerning esophageal cysts is their origin, and several investigators have written excellent reviews of the major hypotheses in that field[4,13] (Table). During

TABLE

Hypotheses Concerning the Origin of Esophageal Cysts
(Taken from M. A. Cassel[1])

1. Origin from embryonic diverticula.
2. Origin from omphalomesenteric system or Vitelline duct.
3. Failure of coalescence of the vacuoles in the transverse axis when the alimentary tube is in the solid stage.
4. Sequestration of embryonic multipotential entodermal cells from the lung bed area of the primitive alimentary analog with later growth and development.
5. Imbalance of organizational substance in embryonic life.
6. Abnormal or isolated twinning theory of origin similar to dermoid and teratomas.

its embryological development sequence, the esophagus is lined with simple columnar, pseudostratified ciliated columnar, and finally stratified squamous epithelium. Esophageal cysts may be lined by any of the above types of epithelium. Classifying the foregut cysts as acquired or congenital on the basis of the epithelial lining is difficult, since more than one type of epithelium may be present in the same cyst. An occasional report of malignancy arising in a cyst has been recorded.[3]

Grossly, esophageal cysts are spheroid and usually do not communicate with the esophagus.[8] Microscopically, the epithelium may be squamous, columnar, or pseudostratified columnar which is commonly ciliated.[2] In the less common double esophagus, the second lumen is lined by normal squamous epithelium, and the wall has normal layers except for intermingling of the outer muscular layer of the common wall.



Fig. 2—Postoperative barium swallow demonstrates essentially normal esophageal contour and passage of barium.

Esophageal cysts in adults are often asymptomatic and are commonly found in the lower half of the esophagus.[11] When symptoms occur, they are secondary to inflammation or infection, at which time they increase in size and cause pain, distortion, and malfunction of the esophagus at the level of the cyst. Patients with symptomatic esophageal cysts usually complain of one or all of the following symptoms: dysphagia, regurgitation, anorexia, weight loss, recurrent episodes of pneumonitis, dyspnea, wheezing or choking episodes.[9,10] The patient reported had dysphagia.

The diagnosis of intramural benign tumors and cysts depends on roentgenographic and endoscopic findings. On roentgenographic studies, an esophageal cyst is represented by a sharply outlined, smooth, ovoid, or lobulated filling defect in the barium-filled esophagus which forms a relatively sharp angle with the adjacent esophageal wall when seen in the lateral or anteroposterior views. On esophagoscopy, the mucosa is intact, overlying a bulging area of the esophageal lumen.[10,12] The right pleural cavity is affected more frequently than the left.[13]

Surgical excision is the treatment of choice. Most duplications of the esophagus can be enucleated without damage to the esophageal mucosa and the muscular wall of the esophagus reconstructed.[10] In the event of larger intramural cysts or duplications of esophagus (a double esophagus), division of the common wall may be required. Esophageal duplications that extend below the diaphragm have been done as a staged procedure.[7,10] Because of associated suppurative changes produced in the adjacent lung by extension of the ulceration and infection in the esophageal cyst a pulmonary resection may be indicated.[13] Excision of esophageal duplications is necessary in order to rule out malignancy.

Even though the patient is suspected of having a benign cyst, exploration is warranted because of the diagnostic uncertainty. The occurrence of complications seems frequent enough to justify operative removal of these cysts.

Conclusion

A 30-year-old diabetic, with an esophageal cyst causing dysphagia, was completely relieved by surgery.

Martin Beard, M.D.*
Demetre M. Nicoloff, M.D., Ph.D.*
Minneapolis, Minnesota

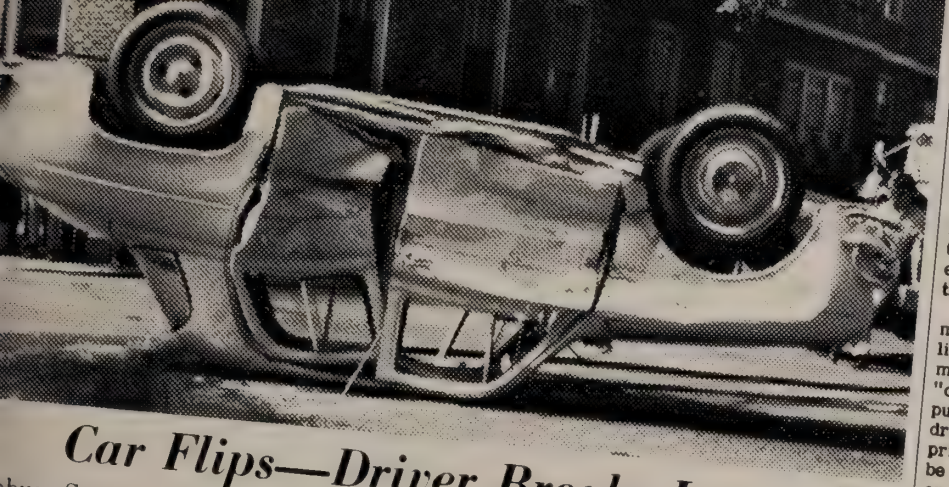
*University of Minnesota Hospitals and Veterans Administration Hospital, Minneapolis, Minnesota.

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4-5. May be secured from the author or the reprints.

Pie: an advance agent of the reaper whose name is Indigestion.—*Ambrose Bierce*



Car Flips—Driver Breaks Leg

...bus, Sept. 7. John P. Jones of Lar... incurred a broken leg today ... driving ... Patrolman B. R. Brown, the car hit a fire hydrant and flipped over on its ... Hasn't ... itar

issue, a... tember t... fications' ... ton dicta... Althou... made Mo... down by a ... ter shar... flat obje... was pass... Board ... McCred... tion" ... elimi... the st... The ... ment ca... limit ra... mile li... "cut-of... public ... dren ... priv... be b... or th... schoo... The ... so so... rathe... hurs...

He's had enough excitement for one day.

For the patient who has been through an accident, the worry and anxiety following the experience may actually heighten the perception of pain. This is why there's a classic 1/4 grain *sedative* dose of phenobarbital in Phenaphen with Codeine—*to take the nervous "edge" off,* so the rest of the formula can control the pain more effectively.

Phenaphen® with Codeine

Phenaphen® with Codeine No. 2, No. 3, or No. 4 contains: *Phenobarbital* (1/4 gr.), 16.2 mg. (Warning: may be habit forming); Aspirin (2 1/2 gr.), 162.0 mg.; Phenacetin (3 gr.), 194.0 mg.; Hyoscyamine sulfate, 0.031 mg.; Codeine Phosphate, 1/4 gr. (No. 2), 1/2 gr. (No. 3), or 1 gr. (No. 4). (Warning: may be habit forming).

THE COMPOUND ANALGESIC THAT CALMS INSTEAD OF CAFFEINATES

Indications: Phenaphen with Codeine provides relief in severer grades of pain, on low codeine dosage, with minimal possibility of side effects. Its use frequently makes unnecessary the use of addicting narcotics. **Contraindications:** Hypersensitivity to any of the components. **Precautions:** As with all phenacetin-containing products excessive or prolonged use should be avoided. **Side effects:** Side effects are uncommon, although nausea, constipation and drowsiness may occur. **Dosage:** 1 or 2 capsules at 2 to 4 hour intervals, or as directed by physician. For further details see product literature.

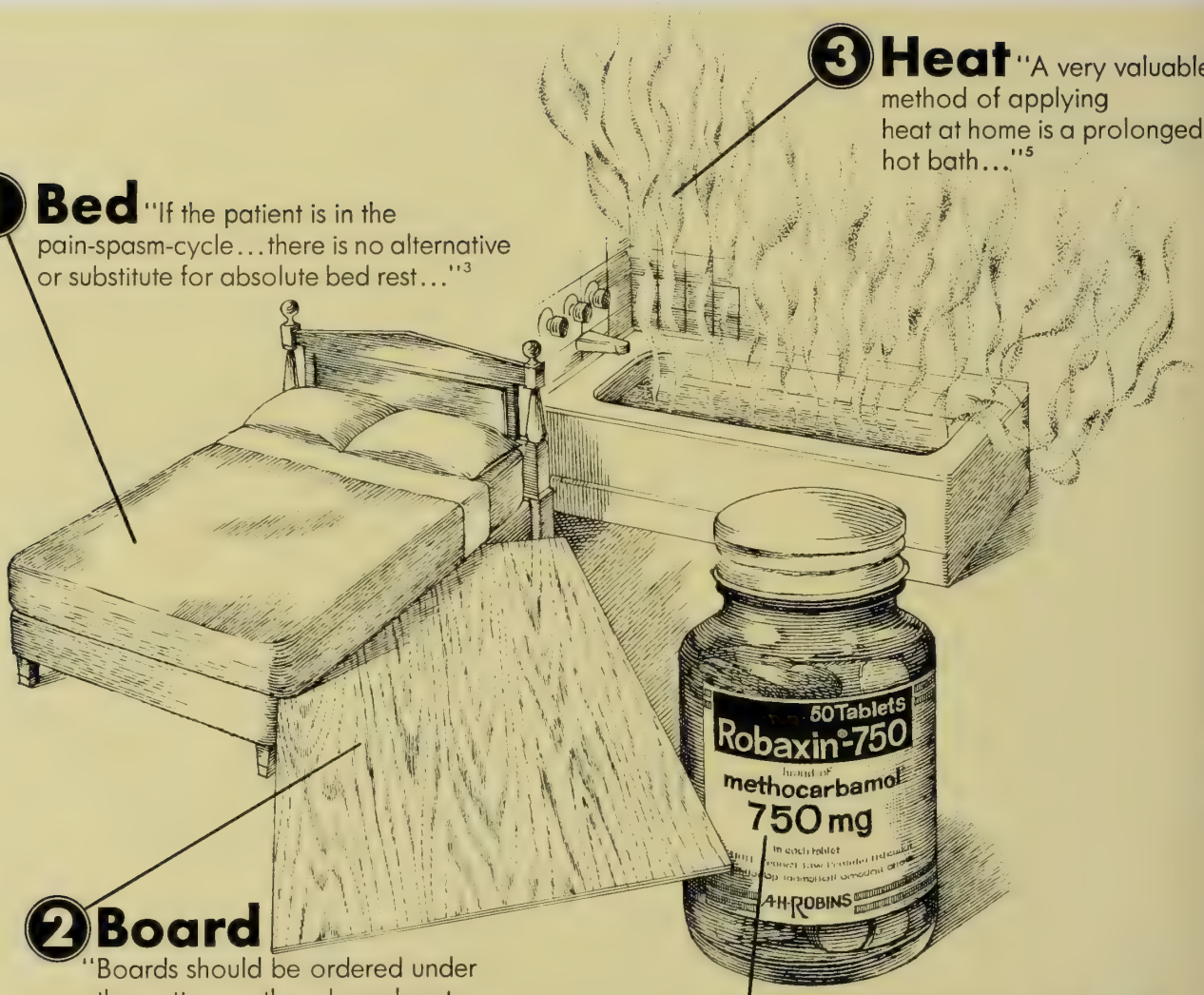
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LOW-BACK PAIN

A CONSERVATIVE, FOUR-POINT PROGRAM

The low back pain that is most frequently seen in general practice is mechanical in nature, i.e., postural back pain, joint dysfunction and acute back strain.[1,2] For this type of discomfort, a conservative regimen is usually sufficient to relieve aches and pains, and to help keep the patient functioning. Components of this basic program include:



1 Bed "If the patient is in the pain-spasm-cycle...there is no alternative or substitute for absolute bed rest..."[3]

2 Board "Boards should be ordered under the mattress...these boards act by immobilizing the spine..."[4]

3 Heat "A very valuable method of applying heat at home is a prolonged hot bath..."[5]

4 Robaxin®-750 (methocarbamol, 750 mg. capsule-shaped tablets) A well-tolerated[6] skeletal muscle relaxant, methocarbamol helps relieve spasm "...without interfering with normal tone and movement."[7] And there is little likelihood of sedation.[6]

Indicated for relief of skeletal muscle spasm. **Contraindicated** in hypersensitive patients. **Side Effects** (lightheadedness, dizziness, drowsiness, nausea) may occur rarely, but usually disappear on reduced dosage. Hypersensitivity reactions develop infrequently. See product literature for further details. **Also available:** Robaxin® Tablets (methocarbamol, 500 mg.) Robaxin Injectable (methocarbamol, 1 Gm./10 cc.)

References: (1). Godfrey, C.M.: Applied Therap. 8:950, 1966. (2). Gottschalk, L.A.: GP 33:91, 1966. (3). Rowe, M.L.: J. Occup. Med. 2:219, 1960. (4). Cozen, L.: South Dakota J. Med. 18:26, 1965. (5). Soto-Hall, R.: Med. Sc. 14:23, 1963. (6). Weiss, M. and Weiss, S.: J. Am. Osteopath. A. 62:142, 1962. (7). Feuer, S.G., *et al.*: New York J. Med. 62:1985, 1962.

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Clinical Path Conference

Mycotic Aneurysms of the Left Ventricle and Ascending Aorta*

Dr. Yang Wang:**

The patient, a 36-year-old white man, had been treated in his home community for bacterial endocarditis for a period of five weeks, during which time coagulase-negative Staphylococcus aureus had been cultured repeatedly from the blood. A month after discharge from the hospital he was admitted to the University of Minnesota Hospitals because of hemoptysis, fever and chills.

Physical examination revealed a febrile, debilitated, dyspneic man. The temperature was 103°F. The blood pressure measured 110 mm. Hg. systolic and 70 mm. Hg. diastolic. There were signs of severe congestive cardiac failure. The maximum cardiac impulse was in the anterior axillary line in the seventh intercostal space and was left ventricular in type. A grade 3/6 pansystolic murmur of tricuspid incompetence was present and, in addition, an early diastolic blowing murmur was audible along the left sternal border. A diastolic gallop was detected at the apex. The pulmonic component of the second heart sound was accentuated. Examination of the lungs revealed signs of consolidation of the lower lobe of the right lung.

The concentration of hemoglobin was 9.0 Gm. per 100 ml. of blood and the total leukocyte count was 16,300 per cu. mm., of which 90 per cent were neutrophils. The erythrocyte-sedimentation rate was 72 mm. per hour (Westergren). The value for blood urea nitrogen was 29 mg. per 100 ml. of blood. Blood cultures were sterile.

The clinical diagnosis was aortic insufficiency, perhaps secondary to perforation of an aortic cusp, with recurrent bacterial endocarditis. Treatment with penicillin, digitalis and diuretics was instituted. Death occurred suddenly five days after admission.

Dr. Elliot Chesler:†

On the patient's admission the electrocardiogram showed first degree A-V block (P-R interval 0.26 sec.) and intraventricular conduction delay of the left bundle branch type. In addition, the sum of the R wave in V_6 and the S wave in V_1 was 51 mm.; this suggested left ventricular hypertrophy. Subsequently the first degree A-V block persisted and left bundle branch block became established (QRS = 0.12 sec.) (Figure 1).

*This study was supported by Public Health Service Research Grant 5 RO1 HE05694 and Research Training Grant 2 T1 HE05570 from the National Heart Institute.

**Associate Professor, Department of Medicine, University of Minnesota, Minneapolis, Minnesota.

†Physician, Cardiac Clinic, Baragwanath Hospital and University of the Witwatersrand, Johannesburg, South Africa, on leave of absence; currently, Research Associate in Cardiovascular Pathology, The Charles T. Miller Hospital, St. Paul, Minnesota; Instructor, Department of Medicine, University of Minnesota, Minneapolis, Minnesota.

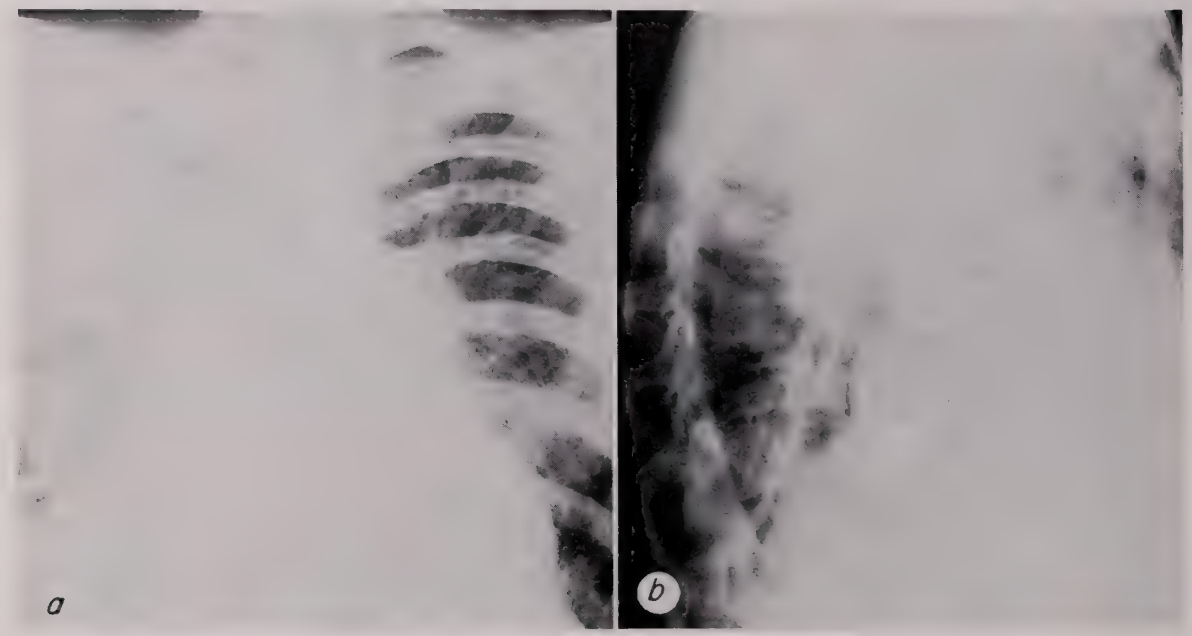


Fig. 1—Roentgenograms of thorax. (a) Posteroanterior and (b) left lateral views.

The thoracic roentgenograms showed left ventricular enlargement and prominence of the ascending aorta and aortic knuckle. Multiple infiltrates, consistent with infarcts, were present in the right pulmonary field (Figure 2).

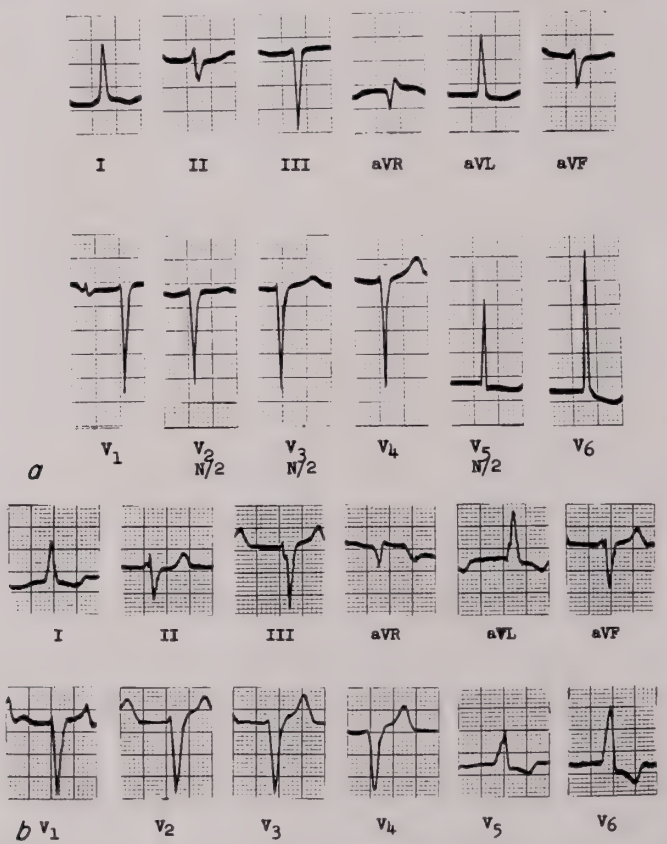


Fig. 2—Electrocardiograms. (a) On admission and (b) three days after admission.

The clinical, radiologic and electrocardiographic features were thus compatible with severe aortic insufficiency. The heart failure was almost certainly precipitated by bacterial endocarditis and aggravated by the occurrence of pulmonary embolism.

The abnormalities noted in the electrocardiogram are of considerable interest. While prolongation of the P-R interval is a not uncommon finding in cases of aortic insufficiency, left bundle branch block is unusual. This combination of abnormalities in conduction suggests a lesion involving the conduction system and may be observed in circumstances unrelated to bacterial endocarditis. This is rheumatoid aortitis and aortic regurgitation with granulomatous involvement of the conduction tissue.[1] There was no evidence of rheumatoid arthritis in our patient. It is tempting to postulate, therefore, that the aortic insufficiency was a result either of a congenital bicuspid aortic valve or rheumatic endocarditis, and that bacterial infection of the valve had resulted in septic emboli to the conduction system.

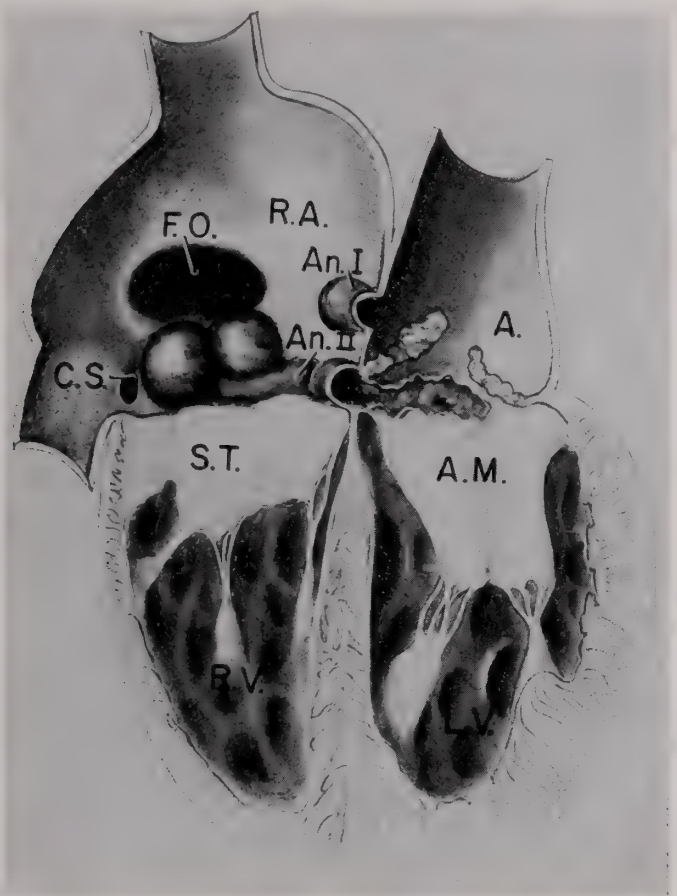


Fig. 3—Drawing representing frontal section of heart revealing interior of right atrium (R.A.), ascending aorta (A.) and right (R.V.) and left (L.V.) ventricles. Above vegetations on partially destroyed aortic valve is a small mycotic aneurysm (An.I) of the ascending aorta. Beneath the aortic valve and at the membranous septum is the mouth of a larger mycotic aneurysm (An.II). The latter extends into the atrial septum to appear as a lobulated structure anterior to the ostium of the coronary sinus (C.S.) and inferior to the fossa ovalis (F.O.). S.T. = septal leaflet of tricuspid valve; A.M. = anterior leaflet of mitral valve.

In dealing with bacterial endocarditis one realizes that renal involvement is not uncommon and in some cases dominates the clinical picture. The level of blood urea was slightly elevated in this patient, suggesting that an element of renal involvement may have been present.

Pathologic Findings

Dr. Michael Korns:*

The heart was enlarged, weighing 700 grams. The increase in weight was mainly on the basis of extreme left ventricular hypertrophy. The focal point of interest was bacterial endocarditis involving a congenital bicuspid aortic valve (Figure 3). Extension of infection from this site resulted in several secondary lesions, two of which were mycotic aneurysms. The smaller of these involved the ascending aorta, and the other involved the membranous portion of the ventricular septum. Both aneurysms extended into the atrial septum.

The aortic valve was composed of two cusps, an anterior and a posterior. A shallow raphe extended from the aortic wall onto the aortic side of the anterior and larger cusp. The active bacterial endocarditis of the aortic valve was represented by a major defect in the posterior cusp, only the commissural aspects of the cusp remaining. Friable vegetations were deposited upon the edges of the defect in the cusp (Figure 4*a*). From the posterior cusp,

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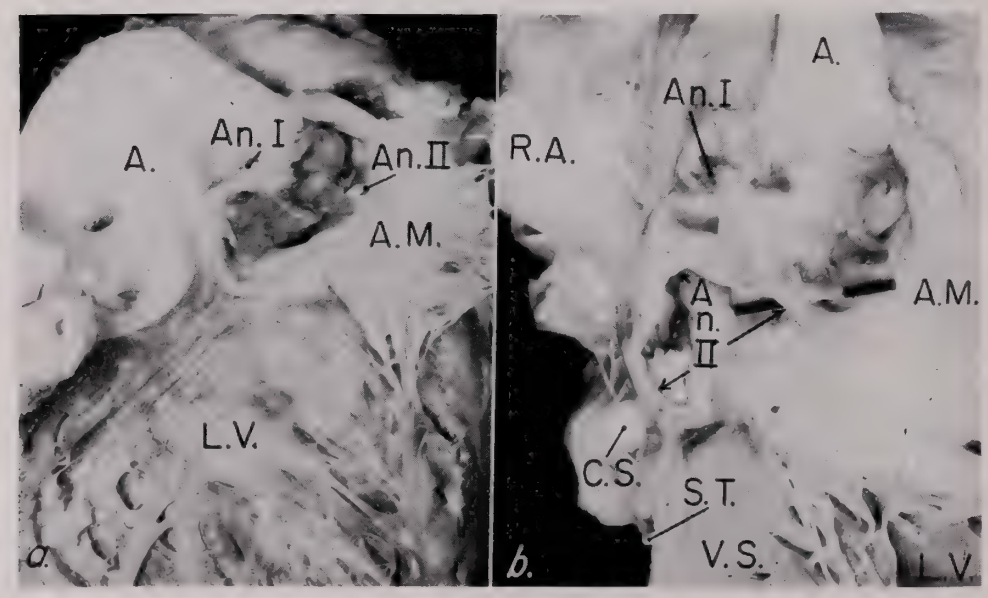


Fig. 4—(a) Ascending aorta (A.), congenital bicuspid aortic valve, and left ventricle (L.V.). At the junction of the anterior leaflet of the mitral valve (A.M.) and the posterior leaflet of the aortic valve the probe is in the ostium of the larger mycotic aneurysm (An.II) which involves the membranous ventricular septum. The ostium of the smaller mycotic aneurysm (An.I), which involves the ascending aorta, is obscured by vegetations covering the nearby aortic cusp. (b) Base of heart in plane of section similar to that in Figure 3 revealing right atrium (R.A.), ascending aorta (A.), aortic valve, and ventricular septum (V.S.). Black probe passes behind remnant of aortic valvular cusp into larger mycotic aneurysm (An.II) which extends to the level of the coronary sinus (C.S.) and encroaches upon the wall of the right atrium (R.A.). A tiny segment of septal leaflet of tricuspid valve (S.T.) is visible beneath the coronary sinus. Smaller mycotic aneurysm (An.I) begins in aorta and also encroaches upon right atrium.

vegetations extended inferiorly to involve the subjacent membranous septum and the base of the anterior mitral leaflet.

A perforation in the membranous septum led into a lobulated aneurysm which lay in the atrial septum and extended to the posterior wall of the right atrium (Figure 4*b*). The aneurysm in the atrial septum measured about 4 x 2 cm., and its two locules bulged into the right atrial cavity (Figure 5).



Fig. 5—Right atrium (R.A.) and right ventricle (R.V.). Two loculi of larger mycotic aneurysm (An.II) bulge against the septal wall of the right atrium between the fossa ovalis (F.O.) and septal leaflet of tricuspid valve (S.T.). Probe is in coronary sinus (C.S.), the ostium of which lies just posterior to the aneurysm.

The most posterior aspect of the aneurysm encroached on, and slightly compressed, the ostium of the coronary sinus. The aneurysm encroached on but did not involve the atrioventricular node (Figure 6).

In addition, a separate aneurysm involved the posterior wall of the ascending aorta. The mouth of the aortic aneurysm measured about 8 mm. in diameter, and its body measured about 1 cm. in greatest dimension. This also presented against the septal wall of the right atrium. The aneurysm of the aorta and that of the membranous septum, although near each other in the atrial septum, did not communicate, nor did the cavity of either aneurysm communicate with the right atrial cavity (Figure 3).

Histologic examination revealed a destructive process involving the aortic valve. Vegetations deposited upon the surface of the valve were incompletely organized and contained bacterial colonies. In each aneurysm the lining was formed by granulation tissue which lay on a layer of dense fibrous tissue (Figure 7). Secondary lesions in the immediate vicinity of the aortic valve included a 1-mm. perforation in the anterior leaflet of the mitral valve. Numerous myocardial infarcts of varying age were found in all portions of the left ventricle.

An incidental finding was a defect in the muscular part of the ventricular septum, 2 mm. in diameter, closed by a fibrous membrane. This was regarded as a spontaneously closed muscular ventricular septal defect. Intrinsically, the tricuspid valve was normal.

The lungs showed chronic congestion, organizing pneumonitis, patchy bronchopneumonia and hemorrhage; and some of the vessels, both arteries and veins, contained thrombi. In addition to the pulmonary congestion, other manifestations of congestive cardiac failure included minimal bilateral pleural effusions and generalized visceral congestion. With respect to the latter, there was widespread centrolobular hepatic necrosis.

Evidence of systemic embolism was the presence of a gross infarct in one kidney and a microinfarct of the pituitary gland.

Summary

Dr. Jesse Edwards:*

Of interest are several features in this case, such as (1) the recrudescence of infection, (2) the congenital bicuspid nature of the aortic valve, (3) the presence of multiple infarcts in the myocardium and (4) the secondary mycotic aneurysms.

Recurrent Infection

When a patient with bacterial endocarditis suffers a recurrence and two

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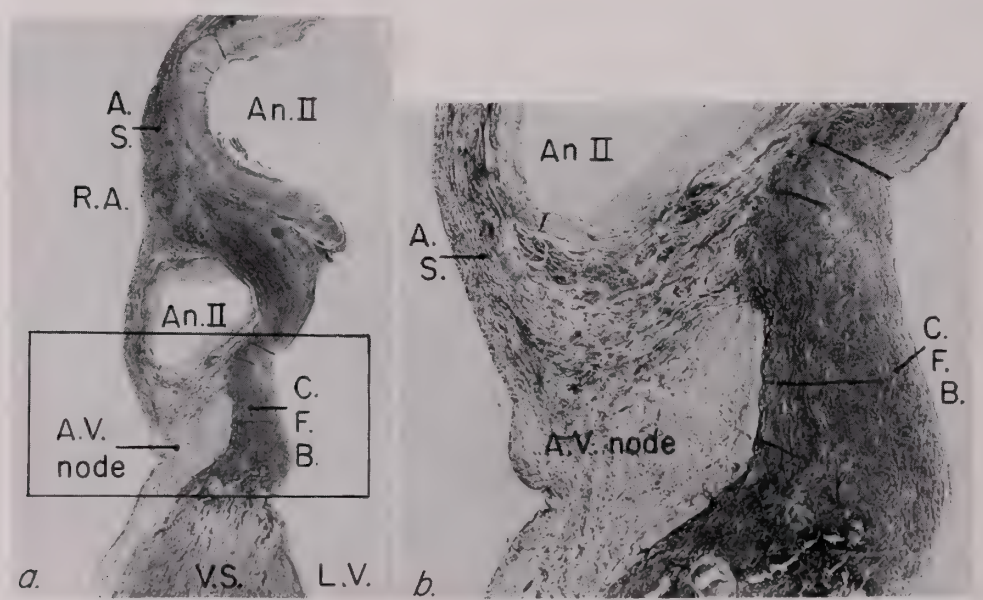


Fig. 6—(a) Photomicrograph of frontal section through base of ventricular septum (V.S.) and adjacent atrial septum (A.S.). Two locules of larger aneurysm (An.II) abut on septal wall of right atrium (R.A.). The lower locule of the aneurysm approaches but does not invade the atrioventricular node which lies in the concavity of the central fibrous body (C.F.B.). Elastic tissue stain; X4. (b) Photomicrograph of that part of *a* enclosed in rectangle. Elastic tissue stain; X14.

separate organisms are involved, it is a simple matter to conclude that reinfection had occurred. When the same organism is obtained in two episodes, such an explanation may be the correct one. Yet one cannot rule out a situation of continuous infection during which the clinical picture suggested arrest of the initial infection. In the case discussed blood cultures positive for Staphylococcus aureus were obtained initially and then cultures yielded no growth. Cultures of the blood yielded negative results during the second admission. The nature of the aortic valvular lesions was such as to indicate that an active infectious process was present at the time of death. It is probable that the original infection had not been completely overcome and that for some reason cultures of the blood yielded no growth even though infection was still active.

One cannot, however, entirely exclude the possibility that the organism observed in the aortic valve was dead and therefore that the infection had been overcome, leaving the patient with a serious mechanical problem in the form of aortic insufficiency.

Bicuspid Aortic Valve

It will be recalled that the aortic valve was congenitally bicuspid. This is a

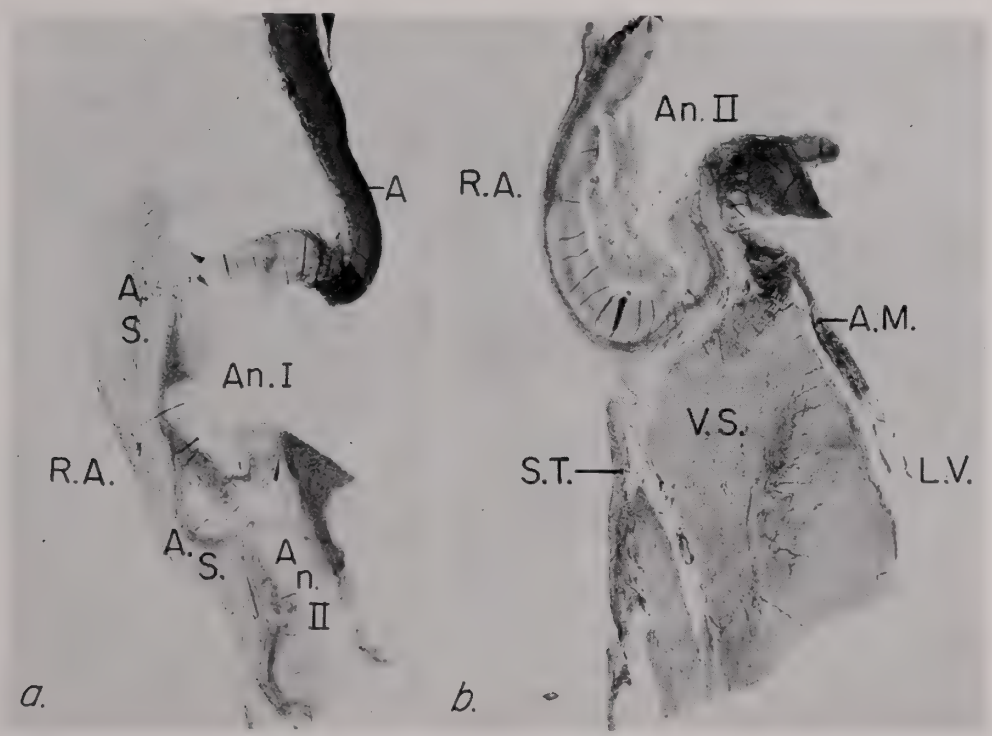


Fig. 7—Low-power photomicrographs of frontal section through aorta and ventricular septum to reveal the ostium of each of the mycotic aneurysms. (a) Extending through the wall of the ascending aorta (A.) is the mouth (An.I) of the smaller aneurysm. The fundus of the latter abuts on the septal wall (A.S.) of the right atrium (R.A.). A small part of the upper portion of the larger aneurysm (An.II) is also shown. Elastic tissue stain; X3. (b) Atrial septum and ventricular septum (V.S.). Larger mycotic aneurysm (An.II) containing exudate abuts on the septal wall of the right atrium (R.A.) above the septal leaflet of the tricuspid valve (S.T.). A.M. = anterior leaflet of mitral valve. Elastic tissue stain; X3.

common predisposing anatomic state for aortic valvular bacterial endocarditis. While many aortic valves that become infected are bicuspid in nature, of these about half are so on the basis of a congenital anomaly of the aortic valve. In the remaining half the basis for this process is antecedent rheumatic fever.

It was clear clinically that the patient was suffering from aortic valvular insufficiency. Pathologically, the destructive nature of the valve would amply explain this valvular disturbance; yet one recognizes that a congenital biscuspid valve may be incompetent without infection. Did this patient have an incompetent congenital bicuspid valve in which the degree of incompetence was accentuated by the destructive effects of the bacterial endocarditis?

The fact that the heart weighed 700 grams would suggest that aortic insufficiency had been present for more than two months, the period during which bacterial endocarditis was evident.

Multiple Infarcts

The multiple infarcts observed in the myocardium are representative of a common occurrence in bacterial endocarditis involving the left side of the heart.[2] Such lesions are to be interpreted as the result of embolism of infective material from the involved valve into the coronary arterial system. While such emboli were not described by Dr. Korns, one must assume that serial sections, including vessels supplying infarcted areas in the myocardium, would reveal such embolic lesions.

Mycotic Aneurysms

Mycotic aneurysms in relation to the aortic valve are more common in instances of aortic bacterial endocarditis than in comparable disease of the mitral valve for two reasons: (1) infective material attached to cusps of the aortic valve may make direct contact with the aortic wall and serve to inoculate areas of such contact with the infecting organism; and (2) the concentration of bacteria is greatest in relation to the valve that is infected.

In relation to the aortic valve, common sites for mycotic aneurysms are the aorta, either at a sinus or in the ascending portion, and the anterior leaflet of the mitral valve. Two such lesions were found in addition to an aneurysm of the ventricular septum. The lesion of the mitral valve had caused a small perforation and had undoubtedly been responsible for mitral insufficiency. This must have been of minor degree, as the perforation in the anterior mitral leaflet was small. The aneurysm of the aorta had not perforated. If it had, one must conclude from its position that it would have led to an aortic-right atrial communication.

The aneurysm of the ventricular septum is of special interest. In the first place such a mycotic aneurysm so extensive as to extend to the posterior aspect of the right atrium is rare. Had this aneurysm perforated, a left ventricular right atrial communication would have resulted. The question may be raised as to the relationship of the aneurysm in the ventricular septum to the observed disturbances in atrioventricular conduction.

The aneurysm was observed to encroach upon but not to involve the atrioventricular node. This would suggest a positive relationship between the anatomic observation and the disturbance in conduction. The conduction tissue is sensitive to mechanical pressures. It is, therefore, possible that increased tissue pressure around the aneurysm may have affected a func-

tional disturbance of the atrioventricular node. Another explanation is that edema of tissues around the focal point of infection may have involved the node to such a degree as to make it malfunctional.

Diagnosis

Mycotic aneurysms of the left ventricle and ascending aorta, complicating aortic valvular bacterial endocarditis.

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Elliot Chesler, M.B., M.R.C.P. (Edin.)*
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On Wine in Acute Diseases

One must determine when sweet, strong, and dark wine should be given in acute diseases. Wherefore the sweet affects the head less than the strong, attacks the brain less, evacuates the bowels more than the other, but induces swelling of the spleen and liver; it does not agree with bilious persons, for it causes them to thirst; it creates flatulence in the upper part of the intestinal canal, but does not disagree with the lower part, as far as regards flatulence; and yet flatulence engendered by sweet wine is not of a transient nature, but rests for a long time in the hypochondria. And therefore it in general is less diuretic than wine which is strong and thin; but sweet wine is more expectorant than the other. But when it creates thirst, it is less expectorant in such cases than the other wine, but if it do not create thirst, it promotes expectoration better than the other. The good and bad effects of a white, strong wine have been already frequently and fully stated in the disquisition on sweet wine; it is determined to the bladder more than the other, is diuretic and laxative, and should be very useful in such complaints; for if in other respects it be less suitable than the other, the clearing out of the bladder effected by it is beneficial to the patient, if properly administered. There are excellent examples of the beneficial and injurious effects of wine, all which were left undetermined by my predecessors. In these diseases you may use a yellow wine, and a dark austere wine for the following purposes: if there be no heaviness of the head, nor delirium, nor stoppage of the expectoration, nor retention of the urine, and if the alvine discharges be more loose and like scrapings than usual, in such cases a change from a white wine to such as I have mentioned, might be very proper. It deserves further to be known, that it will prove less injurious to all the parts above, and to the bladder, if it be of a more watery nature, but that the stronger it is, it will be the more beneficial to the bowels.—*Hippocrates*



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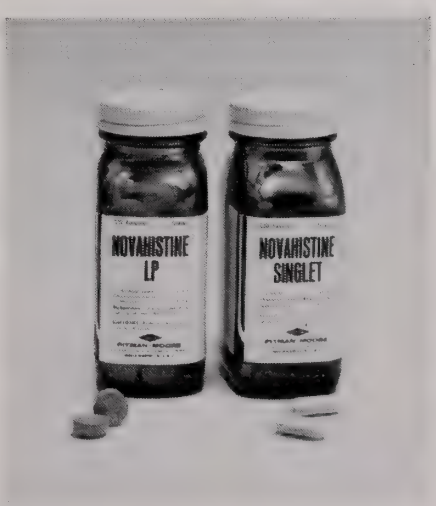
Novahistine Singlet tablets, which provide analgesic-antipyretic effect, as well as decongestant action, are indicated for upper respiratory infections accompanied by pain, aches and fever.

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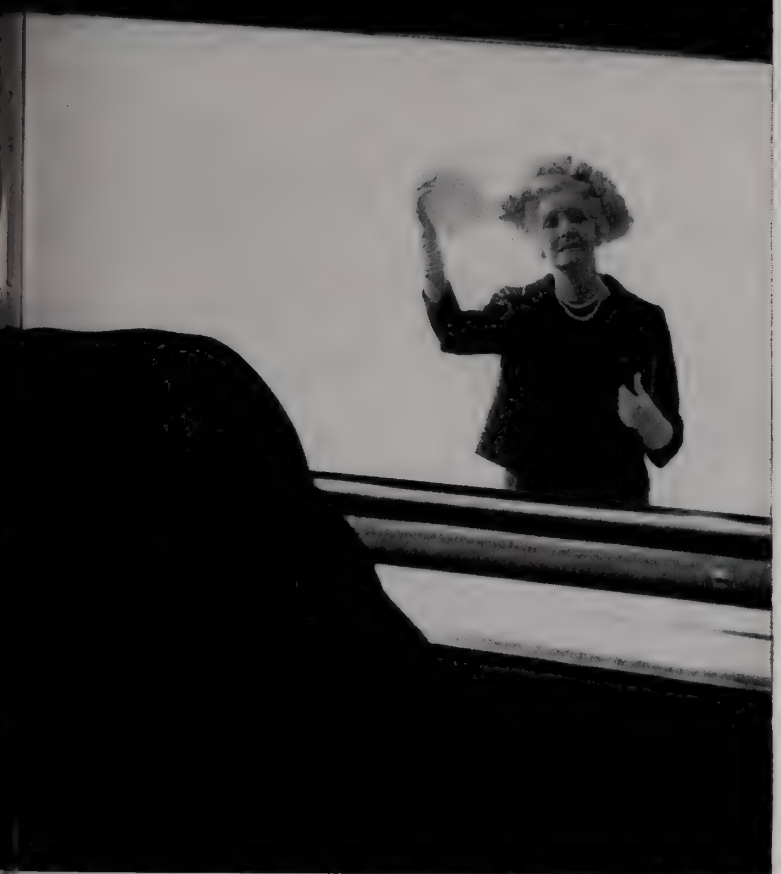


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Indications: Tofrānil is recommended for the treatment of depressive states of diverse psychopathology.
Contraindications: The concomitant use of Tofrānil and monoamine oxidase inhibiting (M.A.O.I.) compounds is contraindicated. Hyperpyretic crises or severe convulsive seizures may occur. Potentiation of adverse effects can be serious or even fatal. An interval of at least 7 days after M.A.O.I. therapy has been discontinued should be allowed before Tofrānil may be substituted. Initial Tofrānil dosage should be low, increases should be gradual, and the patient's progress should be carefully observed.
Warning: Clinical reports have suggested that there may be a risk of teratogenesis associated with the use of this compound during the first trimester of pregnancy. Unless, in the opinion of the prescribing physician, the potential benefits outweigh the possible risks, Tofrānil should not be used during the first trimester of pregnancy.
Cardiovascular complications, including myocardial infarction and arrhythmias, have occasionally occurred in susceptible individuals. Patients with cardiovascular disease should be given the drug only under careful observation and in low dosage.
Precautions: Since suicide is always a possibility in severely depressed patients and one which may persist until significant remission occurs, such patients should be carefully supervised during early treatment with Tofrānil. Some severely depressed patients may also require hospitalization and/or concomitant electroconvulsive therapy.
Because of its anticholinergic effect, caution should be observed in prescribing Tofrānil for patients with increased intraocular pressure.
In rare instances, transient cardiac arrhythmias have occurred in hyperthyroid patients and in patients receiving thyroid medication when Tofrānil was added to the regimen.
Imipramine may block the pharmacologic activity of guanethidine and other related adrenergic neuron-blocking agents.
The drug is not recommended at the present time in patients under 12 yea of age.
Adverse Reactions: Dryness of the mouth, tachycardia, constipation, dis turbances of accommodation, sweating, dizziness, weight gain, urinary frequency or retention, nausea and vomiting, peripheral neuritis, mild parkinson-like syndrome, tremors, rare cases of falling in elderly patients, confusional states (with such symptoms as hallucinations and disorientation), activation of psychosis schizophrenics and agitation (includ

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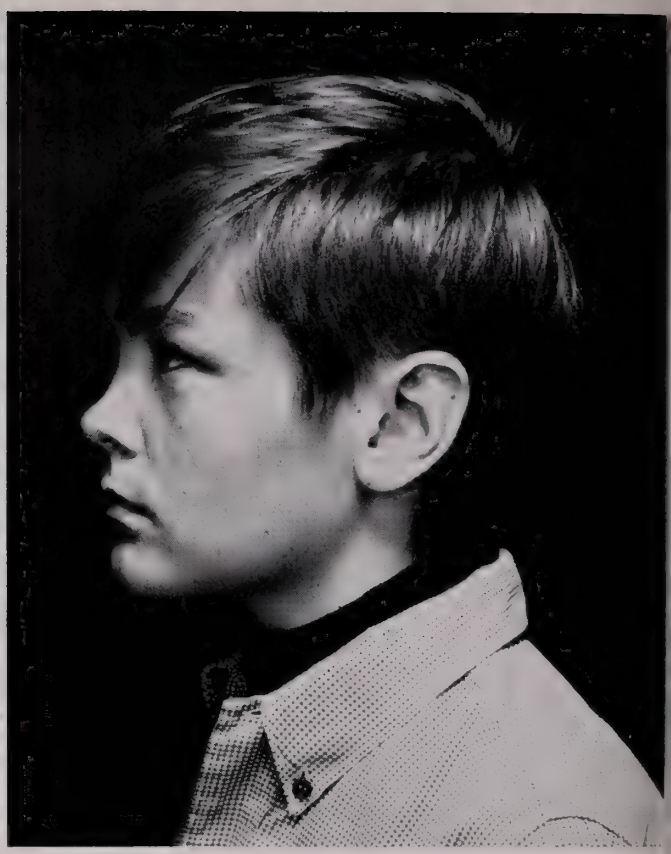
Although toxic reactions severe enough to require discontinuation of Tofrānil are uncommon, in patients with cardiovascular disease, thyroid disorders, increased intraocular pressure, or in those receiving anticholinergics (including antiparkinsonism agents), the special precautions listed in the Prescribing Information should be carefully observed. The use of Tofrānil in patients receiving M.A.O.I.'s is contraindicated.

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ng hypomanic and manic episodes) which may require dosage reduction and/or addition of a tranquilizer or temporary discontinuation of the drug, epileptiform seizures, orthostatic hypotension and substantial blood pressure fall in hypertensive patients, purpura, transient jaundice, bone marrow depression including agranulocytosis, sensitization and skin rash including photosensitization, eosinophilia, and mild withdrawal symptoms on sudden discontinuation after prolonged treatment with high doses. Occasional hormonal effects (impotence, decreased libido, and estrogenic effects) may be observed. Atropine-like effects may be more pronounced (e.g. paralytic ileus) in susceptible patients and in those using anticholinergic agents (including antiparkinsonism drugs).
Outpatient Adult Dosage: Initially, 75 mg. daily, increased, if necessary, to 150 or 200 mg. Maintenance dosage may be lower, 50 to 150 mg. daily, if possible.
Geriatric and Adolescent Dosage: Initially, 30 or 40 mg. daily, which may be increased according to response and tolerance. It is usually unnecessary to exceed 100 mg. daily.
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Dermatology

Shoe Dermatitis

A 30-YEAR-OLD woman had an eruption involving the dorsal aspects of both feet. The dermatitis was well demarcated in a band-like pattern (Figure). The onset of the eruption was traced to a recently purchased pair of sandals. A patch test with 0.25% potassium dichromate (aq. sol.) was positive.

Eruptions which involve the feet may be acute or chronic and can be incapacitating. Many skin diseases manifest themselves on the extremities, the feet in particular. Such conditions as dyshidrotic eczema (neurodermatitis), dermatomycosis, psoriasis, pyoderma, and contact dermatitis are among the more common. Of these diseases, contact dermatitis from shoes is of interest in that it may be very recalcitrant; yet the patient can be helped promptly if the diagnosis is made.



Figure

In making this diagnosis a careful history of the eruption is important, especially the initial site and character of involvement. For example, there have recently been several reports of sandal-strap dermatitis (buffalo hide). This eruption initially shows a strap-like pattern which can aid the clinician in his diagnosis (Figure). The site of onset and the pattern may also be helpful in relating the eruption with the resins, adhesives, and fabrics used as lining material in shoe construction; often multiple materials are used in the construction of a shoe.

Shoe dermatitis may be acute or chronic. It frequently begins on the dorsal aspects of the feet, especially the first toes. With time, the eruption may spread to the other toes, as well as to the dorsal foot and ankle. As a rule, unless severe, the soles and interdigital spaces are not affected, a fact which helps differentiate this condition from a mycotic infection. If the eruption is untreated and becomes acute, it may generalize. In such a situation the hands may develop an "Id"-like eruption which may be vesicular or papular and scaling, to some extent resembling the original dermatitis on the feet.

In shoes there are several components to which an individual may develop a contact allergy, such as rubber accelerators and antioxidants, tannins, dyes, and various synthetic resins. One of the most common causes of shoe dermatitis is the rubber box toe, which accounts for the fact that many of these eruptions begin on the first toe. In the rubber box toe, the rubber accelerators and antioxidants are the usual sensitizers. Monobenzylether of hydroquinone is a common antioxidant offender, while mercaptobenzothiazole and tetramethylthiuram monosulfide are accelerators which are commonly implicated. These substances may also be present in rubber adhesives used in shoes. Of the tannins, chromes and aldehydes may both cause a sensitivity. It should be noted that not all individuals who are allergic to chrome will develop a dermatitis with chrome-tanned leather, for perspiration must be present to remove the chrome from the leather. Another cause of shoe dermatitis are the various dyes, usually after the patient has re-dyed his own shoes, especially the fabric-topped varieties. Dermatitis to the dye of leather shoes is rare, for the dyes used today are quite fast.

Following recognition of this condition, primary treatment consists of controlling the acute phase of the eruption, perhaps by wet compresses, alternated with mild topical steroid ointments. Even if fungal in nature, eruptions of the feet, should not be treated initially with strong ointments (fungicides), for these often exacerbate the condition. If bacterial infection is present, systemic and topical antibiotics may be employed. When the eruption is chronic, hydrocortisone ointments are of value.

An important aspect in the treatment of this condition is the control of perspiration, which can bring into solution such chemicals as the chromes and dyes to produce sensitivity. Control or reduction of perspiration may be achieved by the use of absorbent stockings and various dusting powders. The patient should also be instructed to purchase shoes which are free of the particular factors to which he has shown a sensitivity.

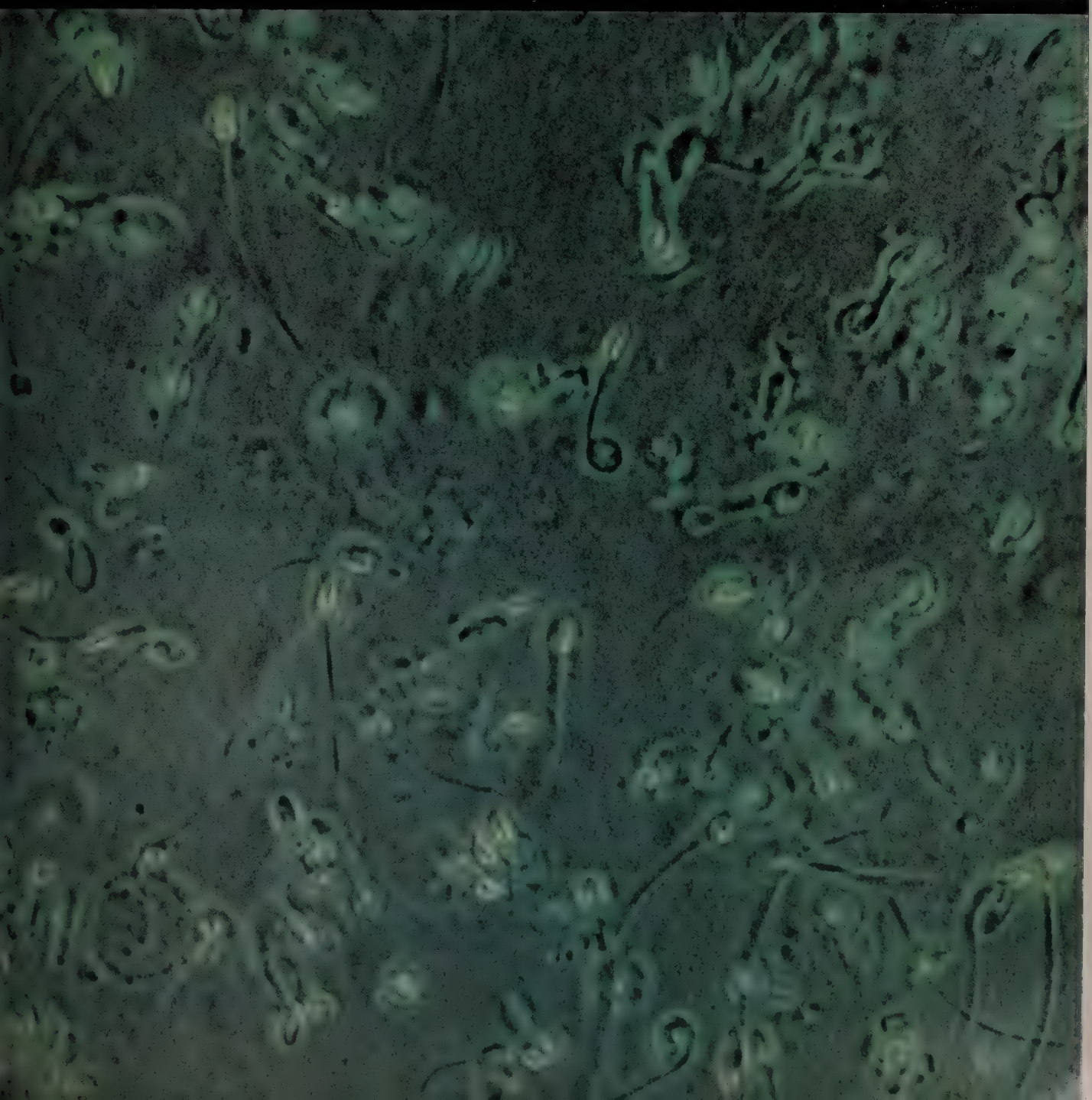
Willard C. Peterson, Jr., M.D.
Minneapolis, Minnesota

Against diseases known, the strongest fence is the defensive virtue, abstinence.
—Benjamin Franklin

When the talk turns to oral contraceptives, it makes medical sense to remember low-dose Norinyl®-1.

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Turn page for contraindications, precautions and side effects.



Reduction of oral contraceptive dosage to the lowest effective levels is a well-accepted principle of conservative medical practice. In keeping with this view, Norinyl is now also available as Norinyl-1, containing exactly one half the previous dosage of norethindrone and mestranol. Clinical experience has established that effective fertility control can be achieved with the same degree of reliability and safety with new Norinyl-1 when taken as directed.

What about switching patients from higher dosage forms?

In transferring patients to low-dose Norinyl-1 from higher-dosage oral contraceptives, some breakthrough bleeding may occur in the early cycles. In the majority of cases the bleeding episode is mild and self-limited. The long-term advantages of the lower dosage form should be weighed against the inconvenience of possible breakthrough bleeding in the individual patient.

Contraindications: 1. Patients with thrombophlebitis or with a history of thrombophlebitis or pulmonary embolism. 2. Liver dysfunction or disease. 3. Patients with known or suspected carcinoma of the breast or genital organs. 4. Undiagnosed vaginal bleeding.

Warnings: 1. Discontinue medication pending examination if there is sudden partial or complete loss of vision or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn. 2. Since the safety of NORINYL-1 (norethindrone 1 mg. with mestranol 0.05 mg.) in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. 3. Detectable amounts of the active ingredients in oral contraceptives have been identified in the milk of mothers receiving these drugs. The significance of this dose to the infant has not been determined.

Precautions: 1. The pretreatment physical examination should include special reference to breast and pelvic organs, as well as a Papanicolaou smear. 2. Endocrine and possibly liver function tests may be affected by treatment with NORINYL-1. Therefore, if such tests are abnormal in a patient taking NORINYL-1 it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, preexisting uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions that may be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. NORINYL-1 should be used with caution in patients with a history of cerebrovascular accident. 6. In relation to breakthrough bleeding, and as in all cases of irregular bleeding *per vaginam*, nonfunctional causes should be borne in mind. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated. 7. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 8. Any possible influence of prolonged NORINYL-1 therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. 9. A decrease in glucose tolerance has been observed in a small percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving NORINYL-1 therapy. 10. Because of the occasional occurrence of thrombophlebitis and pulmonary embolism in patients taking oral contraceptives, the physician should be alert to the earliest manifestations of the disease. 11. Because of the effects of estrogens on epiphyseal closure, NORINYL-1 should be used judiciously in young patients in whom bone growth is not complete. 12. The age of the patient constitutes no absolute limiting factor, although treatment with NORINYL-1 may mask the onset of the climacteric. 13. The pathologist should be advised of NORINYL-1 therapy when relevant specimens are submitted.

Side effects observed in patients receiving oral contraceptives: The following adverse reactions have been observed in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea, edema, chloasma or melasma, breast changes (tenderness, enlargement and secretion), change in weigh (increase or decrease), changes in cervical erosion and cervical secretion suppression of lactation when given immediately postpartum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals, mental depression.

Although the following side effects have been reported in users of oral contraceptives, no cause and effect relationship has been established: anovulation post-treatment, premenstrual-like syndrome, change in libido, changes in appetite, cystitis like syndrome, headache, nervousnes dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodo sum, hemorrhagic eruption, itching.

The following occurrences have been observed in users of oral contraceptives (a cause and effect relationship has been neither established nor disproved): thrombophlebitis, pulmonary embolism, neuro-ocular lesions.

The following laboratory results may be altered by the use of oral contraceptives: increased sulfobromophthalein and other hepatic function tests, coagulation tests (increase in prothrombin, Factors VII, VIII, IX and X), thyroid function (increase in PBI and butanol extractable protein-bound iodine and decrease in T^3 values), metyrapone test, pregnanediol determination.

norethindrone — an original steroid from
SYNTEX
LABORATORIES INC., PALO ALTO, CALIF.

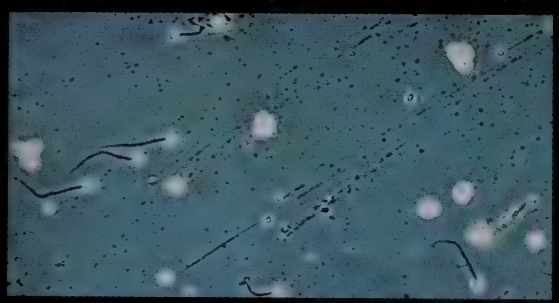
Here's why Norinyl-1 makes medical sense.

The effectiveness of Norinyl-1 as a low-dose oral contraceptive may be explained by its possible multiple action. In addition to its primary action of suppression of ovulation, Norinyl-1 may offer additional protective mechanisms... (1) creation of a cervical mucus that may be hostile to sperm penetration, and (2) development of an endometrium that may be out of phase with nidation. These effects are illustrated below.

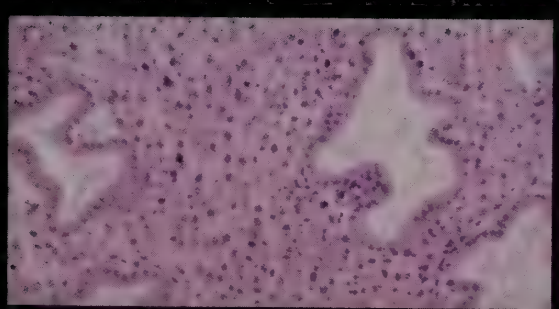
Untreated Patient



Cervical mucus at midcycle is usually thin and watery, with Spinnbarkeit (stretchability) of 15 to 20 cm.

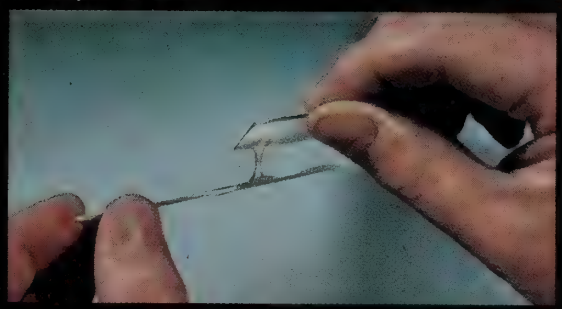


Spermatozoa appear healthy, active, freemoving.

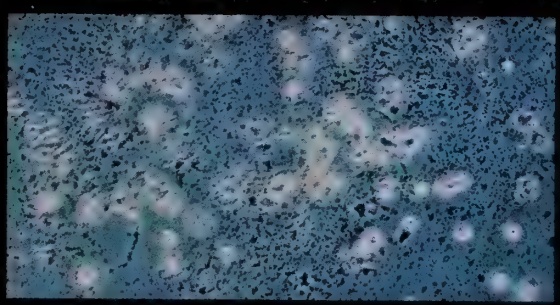


Endometrium of untreated patient is receptive to the fertilized ovum during secretory phase.

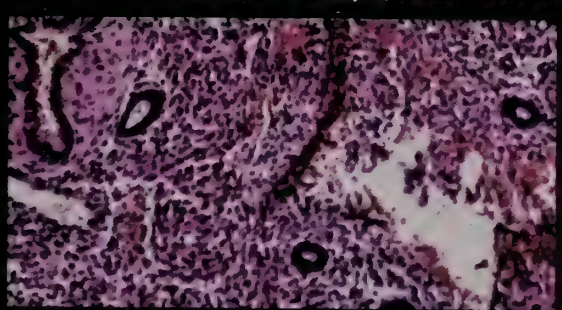
Norinyl-1 Patient



Cervical mucus at midcycle is scanty, viscous—with Spinnbarkeit of 1 cm. or less.



Immobile spermatozoa as they appear in cervical mucus taken from patient treated with Norinyl-1.



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6/67 Q-706A



Grand Rounds

Pulmonary Embolism*

DAVID G. CONNOR, M.D.
Medical Resident

"It is of use from time to time to take stock, so to speak, of our knowledge of a particular disease, to see exactly where we stand in regard to it, to inquire what conclusions the accumulated facts seem to point to, and to ascertain in what direction we may look for fruitful investigations in the future."

Sir William Osler[1]

PULMONARY EMBOLISM is both a common disease and an uncommonly proven diagnosis. We should be concerned with this disease because it is preventable, it is treatable, it is reversible, and because most cases of fatal pulmonary embolism occur on the general medical service. We should define and emphasize clinical aspects of the disease because most often the diagnosis is made primarily by suspecting the disorder and only secondarily by the various laboratory measures available for confirmation. We should be eager to gain knowledge about pulmonary embolism because the phenomenon is so often integrated with the course of other disease states. Lastly, we should fear the disease because of the very nature of our anatomy; the lungs serve as a nonrenewable filter catching all manner of particulate matter, and we are all subject to pulmonary embolism.

I should like to emphasize the diagnosis of pulmonary thrombo-embolism, touching only briefly on pathogenesis and treatment. I will begin with a case report.

Case Report

A 39-year-old negro mother of seven had been well until the age of 22, when she developed symptoms and signs of rheumatoid arthritis. The disorder was severe and she was treated for nine years with various combinations of corticosteroid preparations

*Presented as a Medical Grand Rounds at Hennepin County General Hospital, October 2, 1967.

with good results; but she developed a severe weakness, with wasting of musculature which resulted in her nearly complete immobilization. During hospitalization for diagnosis of this myopathy, the patient developed pleuritic chest pain followed by clinical evidence of thrombophlebitis of the right leg. A chest x-ray showed a slight infiltrate in the right base; and a total lactate dehydrogenase determination reached 2081 international units (heat stable was 810 units) before falling to normal. A lung scan was not done.

The patient was placed in deep Trendelenburg position and treated with intravenously administered heparin. Recovery was unremarkable and she was discharged on dicumarol.

The prothrombin time, however, did not consistently remain in therapeutic range, and six weeks after discharge the patient again developed thrombophlebitis of her leg and shortness of breath. Pleuritic chest pain was present and a chest x-ray suggested the presence of pulmonary infarct on the left. Physical examination revealed dullness to percussion over this area, and a lung scan showed some diminution in radioactivity of the left lung. Lactic dehydrogenase determinations were not elevated, and the patient again responded to rest, heparin and heat packs. She has been asymptomatic since discharge on anticoagulants.

I feel that the most important points to emphasize here are that the clinical and laboratory findings do not always correlate with each other and that pulmonary embolism remains largely a clinical diagnosis based on a high degree of suspicion.

Historical

Läennec[2] described pulmonary apoplexy in 1819 as several small swollen indurations, usually very dark red and occurring in each lung in patients dying from cardiac lesions. In 1855 Rokitansky[3] postulated the embolic origin of these "hemorrhagic infarcts," but it remained for Virchow[4] in 1856 to place foreign bodies in the veins of dogs and to recover these from the pulmonary arteries. Homans[5] in 1934 associated thrombosis with stasis in leg veins, and Hampton and Castleman[6] explored the situation in 1940 and concluded that pulmonary thrombo-embolism occurred commonly in debilitated, old and cardiac patients and was not exclusively a post-surgical disease.

Incidence

Pulmonary embolism accounts for over 300,000 hospital admissions each year; the yearly death rate in the United States is about 47,000 persons, although three times more deaths may occur in which pulmonary embolism has played a significant role.[7] Uhland[8] reported on 981 consecutive autopsies in a general hospital and found 118 cases of pulmonary embolism (12%), while Smith[9] reviewed the autopsies at Peter Bent Bringham in 1963 and confirmed this finding. Emboli were of various ages and sizes in 75% of the cases and were located in more than one region of the lung in the majority of patients. Wagner[10] found most of the emboli in the lower lung fields (60% to the right and 52% to the left), and Smith observed only 10% of the emboli to be associated with pulmonary infarction. Boyd[11] showed that 85% of fatal pulmonary embolism occurred in patients older than forty years and 60% in patients older than sixty.

The experience at Hennepin County General Hospital has shown that in the past 18 months, of the 717 autopsies performed, pulmonary embolism was regarded as the primary cause of death in four percent. This does not represent all deaths in the hospital and does include the medical examiner cases.

The Embolus

It is general consensus that an embolus from the heart or peripheral vein is the primary lesion in pulmonary thrombo-embolic disease.[11,12] Many authors

have sought to define the exact nature of such an embolus, the conditions from which it arose, and its effect on the pulmonary vasculature. These findings become of basic importance in the management of the patient.

Pneumonectomy is well tolerated in the normal man, tidal volume and oxygen exchange remaining nearly normal.[13] Why then should a pulmonary embolus be so disastrous? First, the usual candidate for a pulmonary embolus is not a normal man, but one who has underlying cardiac and/or respiratory disease. Second, Gorham[14] found that in 85% of cases at autopsy, pulmonary emboli were present in the opposite lung from the larger lesion. Third, Dexter[15] showed that by introducing small beads into the arteriolar branches of the pulmonary artery, he was able to produce a marked vasoconstriction, the result of secondary reflex mechanisms. This latter phenomenon has also been shown by Moore et al.[16] who were able to markedly reduce mortality in dogs subjected to embolization by pretreatment with ganglionic blocking agents. The subsequent vasodilatation allowed emboli to escape from the arteriolar bed into the capillary bed which, with its vastly larger total volume, required much more embolization to produce the same degree of disability. The vasoconstrictor long implicated in man has been serotonin, presumably released from the clot wedged into the pulmonic tree. This, then, plus the effect of the mechanical obstruction, the bilateral lesion, and the previously injured lung account for the high morbidity with a pulmonary embolus.

The exact predisposing circumstances to emboli formation are at best confusing. Slowing of the blood per se will usually not cause thrombus formation but this, combined with interference of the clotting mechanism and/or the structure of the vascular endothelium, can produce clot. Deykin in an excellent article on thrombogenesis[17] has suggested that some undetermined factors activate the intrinsic coagulation mechanism, producing a "hypercoagulable state," which, combined with stasis, results in formation of a red thrombus. The stasis in turn becomes important because it prevents dilution of the activated coagulation factors and their clearance by the liver.

Actual clotting of blood may be increased in many clinical situations: hemolytic states, acidosis, pregnancy, and endotoxin shock, to mention the more common. Blood flow is markedly slowed in cases of arterial hypotension, arteriolar vasoconstriction, histamine dilatation of all capillaries simultaneously, and opening of arteriovenous shunts. One can easily postulate how any combination of the above could cause red thrombus formation.

Many disease states predispose to and result in an increased incidence of pulmonary embolism: increasing age, confinement to bed, congestive heart failure, trauma, chronic thrombophlebitis, chronic lung disease, hemiparesis, chronic pyelonephritis, the postoperative state and subacute bacterial endocarditis. These are mentioned to persuade the reader to consider pulmonary emboli as the cause of unexplained dyspnea, fever, tachycardia or hemoptysis in such clinical situations where early recognition and treatment of embolism is very important.

Clinical Diagnosis

The clinical diagnosis of a significant pulmonary thrombo-embolic disorder depends on suspecting the existence of the disease and then correlating the multitude of findings that may exist. The classic triad of shortness of breath, chest pain, and hemoptysis is found in only three percent of major embolic episodes.[18] The Table shows that death is not always immediate, leaving time for careful diagnosis and institution of therapy.

TABLE*

Time from Onset to Death	Percent Cases
10 min. or less	41
15 min.	3
15 min. to 2 hrs.	22
2 hrs. to 12 hrs	8
12 hrs. to 24 hrs.	8
24 hrs. to 48 hrs.	6
3 days to 14 days	7
	(100 cases)

*From Gorham, L. W.[14]

The most common mistaken diagnosis is acute myocardial infarction; the second is stroke, because of the frequent picture of collapse, convulsion and hemiplegia.

Physical Examination

Particular physical findings have been appreciated in patients having an acute pulmonary thrombo-embolism. An initial pulsation in the second left intercostal space may be present because of the obstruction of the pulmonary artery. Many authors have noted a greatly accented pulmonary second sound which disappears with the appearance of right heart failure. Rales are uncommon. A pseudopericardial friction rub in the left second intercostal space may be present and may be confused with that occurring in myocardial infarction. Partial stenosis of the pulmonary artery by the obstructing embolus may produce a systolic murmur in the pulmonic area. An interscapular bruit is a rare finding but has been found in cases in which an embolus overrides the bifurcation of the pulmonary artery. The lung affected by an embolus in its main pulmonary artery may exhibit diminished expansion and an area of increased cardiac dullness to the right of the sternum, apparently due to acute right heart failure. Distended neck veins, a gallop rhythm, and an enlarged liver are frequent findings if acute right heart failure is present. Furthermore, cyanosis, pallor, dyspnea, apprehension, and tachypnea are also common. The disease should be particularly suspected if phlebitis is present (with or without the aid of Homan's sign[20] or the Lowenberg test,[21]) if the patient is febrile or if a pulmonary consolidation is present.

X-Ray Findings

There is no pathognomonic radiologic sign of pulmonary embolism. X-rays help if they are positive for any of the following signs as outlined by Fleischner:[22]

1. Oligemia of the lung fields.
2. Pleonema of the contralateral lung.
3. Evidence of right ventricular enlargement.
4. Dilated hilar arteries.
5. Dilated pulmonary artery trunk.
6. Right-sided inflow stasis with dilatation of the azygous vein and superior vena cava.

The pulmonary infarct is probably the most distinct sign of pulmonary embolus, occurring as a spindle-shaped consolidation along a pleural surface. The classically described "triangular shadow" is uncommonly seen because of the rich pulmonary collateral blood supply.[23]

Electrocardiographic Findings

The electrocardiographic evidence for pulmonary embolism is very useful but not specific. Only 10% to 20% of patients with pulmonary embolism will have electrocardiographic changes consistent with their disease;[24] however, many non-embolic diseases can be ruled out.

The principal findings include a deep S wave in Leads I, V_5 and V_6 with high-peaked P waves in Leads II and III representing acute cor pulmonale; a prominent Q wave in III with inversion of the T wave in II, III and the inner right-sided precordial leads; ST segment depression in I, II, III with staircase ascent of ST in II, suggestive of coronary insufficiency; and acute right axis deviation. Other more non-specific findings include sinus tachycardia (48%), sudden onset of arrhythmia (38%), conduction disturbance (5%), S wave in I, II, III (5%), and clockwise rotation of the heart (5%).

Laboratory Findings

Snodgrass et al.[25] have reported on the value of a triad of laboratory results: the lactic dehydrogenase (LDH), the serum glutamic oxylacetic transaminase (SGOT) and the serum bilirubin, in pulmonary thrombo-embolism. These investigators showed that the serum glutamic oxylacetic transaminase was occasionally elevated because of acute liver congestion but in most cases remained normal, while the lactic dehydrogenase was elevated in 97% and the serum bilirubin in 73% of autopsy-proved cases. Amador[26] measured lactic dehydrogenase by the forward (lactate-to-pyruvate) spectrophotometric method and found an extremely close correlation between an elevated lactic dehydrogenase and a positive lung scan. He also found normal lactic dehydrogenase values in diseases that predisposed to pulmonary embolism, such as congestive heart failure, trauma, thrombophlebitis and the postoperative state, and recommended following patients predisposed to embolic disease with lactic dehydrogenase determination to detect early signs of embolic infarction.

Lung Scan

A recent innovation for diagnosis of pulmonary embolism is radioisotope lung scanning as described by Wagner,[27] whereby radio-iodinated human serum albumin is injected intravenously and accumulates in the lungs. The positive pulmonary scan reveals areas of underperfusion and becomes especially important if there is no infiltrate on chest x-ray. Many have criticized the procedure because it cannot conclusively confirm the diagnosis and many false positive and negative studies occur;[28] however, the lung scan is safe, easy, and relatively economical; also it is more accurate than pulmonary angiography in detecting the small, peripheral or multiple lesions and can be used repeatedly in the same patient to follow return of pulmonary blood flow.[29]

Angiography

Simon and Sasahara[30] have described the technique of selective pulmonary angiography for the diagnosis of pulmonary emboli and emphasize the necessity for making a definitive diagnosis if surgical treatment is contemplated. Multiple angiographic features were noted—among them: obstruction of a pulmonary artery, irregular filling defects and plaques along vessel walls, regional decrease of flow rate of contrast medium, avascular areas, and

proximal dilatation of arteries with emboli. Sautter[31] has performed 150 pulmonary angiograms annually for the past two years in patients with suspected pulmonary embolism and reports a 90% incidence of positive studies. He stresses his unwillingness to operate and/or use the newer fibrinolytic agents without initial angiographic proof of existence of the embolus.

Pulmonary Function

Robin[32] has advocated measurement of the difference in the arterial and end-tidal alveolar carbon dioxide tensions. Any discrepancy greater than three mm. mercury is considered significant and suggests pulmonary embolism.

He also noted arterial oxygen unsaturation in patients with pulmonary embolism (63-90% in his series), an extremely uncommon finding in patients with acute myocardial infarction.

Natural History of the Disease

Multiple minute pulmonary emboli occur throughout a lifetime and remain inconsequential. But the embolus becomes significant when it occludes a large portion of the lungs (estimated at over 60 percent), when it causes reflex vasoconstriction, or when it produces pulmonary infarction. Sautter[33] has documented spontaneous resolution of pulmonary emboli in eight cases and noted resolution in as little as eleven days and as long as 128 days. Wagner[29] has demonstrated nearly complete return of pulmonary flow in most cases in four months.

Many emboli do not resolve, however, and their[8] effect is cumulative, eventually evolving to pulmonary hypertension.[34] In the acute state, Del Guercio[35] has shown that death is likely in the patient with a mean right ventricular pressure greater than 22 mm. mercury secondary to pulmonary embolus. Hopefully, earlier diagnosis and consequent earlier therapy will decrease the mortality rate.

Management

Trendelenburg[36] performed the first pulmonary embolectomy in 1908. Management falls into three broad categories: preventive, medical, and surgical, but all are interrelated; for it is in the best interest of the patient that medical and surgical teams not isolate their therapeutic armamentarium.

Prophylactically, the prevention of immobilization, hemoconcentration and vascular stasis is important. Medically, heparin, given intravenously, appears to be the drug of choice despite the lack of carefully controlled studies on its efficacy.[38] Its rapid onset of action, its easy reversibility, and its antiserotonin and undetermined antiplatelet agglutination action make it ideal in the therapy of pulmonary embolism. Local heat therapy and dextran for peripheral thrombophlebitis, bed rest in Trendelenburg position, and anticoagulation with bishydroxycoumarin are generally accepted measures.

Direct embolectomy was greatly advanced with the advent of successful cardiopulmonary bypass,[39,40] but inferior vena caval ligation has remained the procedure of choice for the patient tolerating his pulmonary embolus well, in whom recurrence is imminent or in whom the disease is bilateral.[41]

More recently an enzyme, urokinase, has been used for the treatment of pulmonary emboli.[42] This is a potent plasminogen activator which can produce clot lysis in vitro and in vivo and has been shown by Sautter to hasten

the lytic process in emboli. In his hands, the infusion of urokinase was a benign procedure and produced dramatic results in thirty patients with pulmonary emboli.

Conclusion

Successful therapy of pulmonary embolism depends on successful diagnosis of the disease. The symptomatic patient cannot usually tolerate further insult to his pulmonary vasculature. Many newer methods for diagnosis and for therapy are at our disposal and we must be prepared to use these if we are to successfully lower current incidence and mortality of pulmonary embolic disease.

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15-42. May be secured from the Grand Rounds Editor.

Cybernetics and Prostheses

There is some work being done on artificial limbs in Russia, in the United States, and elsewhere by a group to which I belong. This work is much more interesting in principle and really makes use of cybernetical ideas.

Let us suppose that a man has lost a hand at the wrist. He has lost a few muscles that serve chiefly to spread the fingers and to bring them together again, but the greater part of the muscles that normally move the hand and the fingers are still intact in the stump of the forearm. When they are contracted, they move no hand and fingers, but they do produce certain electrical effects known as action potentials. These can be picked up by appropriate electrodes and can be amplified and combined by transistor circuits. They can be made to control the motions of an artificial hand through electric motors, which derive their power through appropriate electric batteries or accumulators, but the signals controlling them are sent through transistor circuits.

Such artificial hands have already been made in Russia, and they have even permitted some hand amputees to go back to effective work. This result is facilitated by the circumstance that the same nervous signal which was effective in producing a muscular contraction before the amputation will still be effective in controlling the motor moving the artificial hand.

Thus there is a new engineering of prostheses possible, and it will involve the construction of systems of a mixed nature, involving both human and mechanical parts.*

---

*Norbert Wiener: God and Golem, Inc., M.I.T. Press, 1964.

Mr. President—Your Health*

James A. Garfield, 1831-1881

The health history of our twentieth President, James A. Garfield, can be telescoped into four distinct onslaughts against his constitutional integrity.

The first occurred when young James was a husky fifteen-year-old working on a canal boat. While still lacking the coordination and agility required for his job he accidentally tumbled into the water fourteen times. After his last submersion he became so ill with ague that he had to be sent home to be nursed by his mother. Her home remedies not availing, a distant doctor was sent for, who proceeded to ptyalize the stricken youth with heavy doses of calomel; whereupon young James developed a hard, inflamed bunch on his left side, so sensitive as to practically immobilize him: an "ague-cake" his mother called it. Only after weeks of confinement to his bed did he fully recover his pristine health.

The second assault against Garfield's constitution consisted of camp fever, that ubiquitous scourge of army life, while he was a member of the 42nd Ohio Regiment in the Civil War. For lack of specific treatment, such ineffectual modalities were resorted to as bathing, soaking the feet, and swallowing "hygiene pills." For Garfield this trying period of military service was not only a debilitating but also a disillusioning one. "At the end of his army service he had nothing to show except the rank of brigadier general, a damaged constitution, and a profound distrust of the ability and real political loyalty of the officers under whom he served."

During the presidency Garfield's constitution registered the full impact of the stress and strain imposed by the political responsibilities and moral obligations of his high office. The price exacted was obstinate insomnia which was finally overcome only by increased outdoorsmanship: riding and walking in the open air.

Finally, in a Washington railroad station as he was preparing to depart on a vacation journey July 2, 1881, two assassin's bullets presented the fourth challenge to Garfield's physical integrity. One bullet merely grazed his right arm; the other tore into his back, ravaging his interior with baffling and sinister complications for over two months before death released him from his crucible of suffering.

"The immediate cause of Garfield's death was for some time a matter of dispute among physicians, but those who were in charge . . . made a post-mortem examination the day after his death. The operation was performed by Dr. Lamb, and it was found that the ball, after fracturing the right eleventh rib, had passed through the spinal column in front of the spinal canal. It had fractured the body of the first lumbar vertebra, driving a number of small fragments of bone into the adjacent soft parts, and had lodged just below the pancreas . . . and behind the peritoneum, where it had become completely encysted. The immediate cause of death was a secondary hemorrhage from one of the mesenteric arteries adjoining the track of the ball.

"The primary cause was septicemia with metastatic abscesses. Contributing causes were: (1) rupture of a mesenteric artery by the bullet; (2) bronchopneumonia, and (3) coronary thrombosis."

*With acknowledgment to and quotations from Karl C. Wold, M.D.: Mr. President—How Is Your Health? Bruce Pub., 1948.

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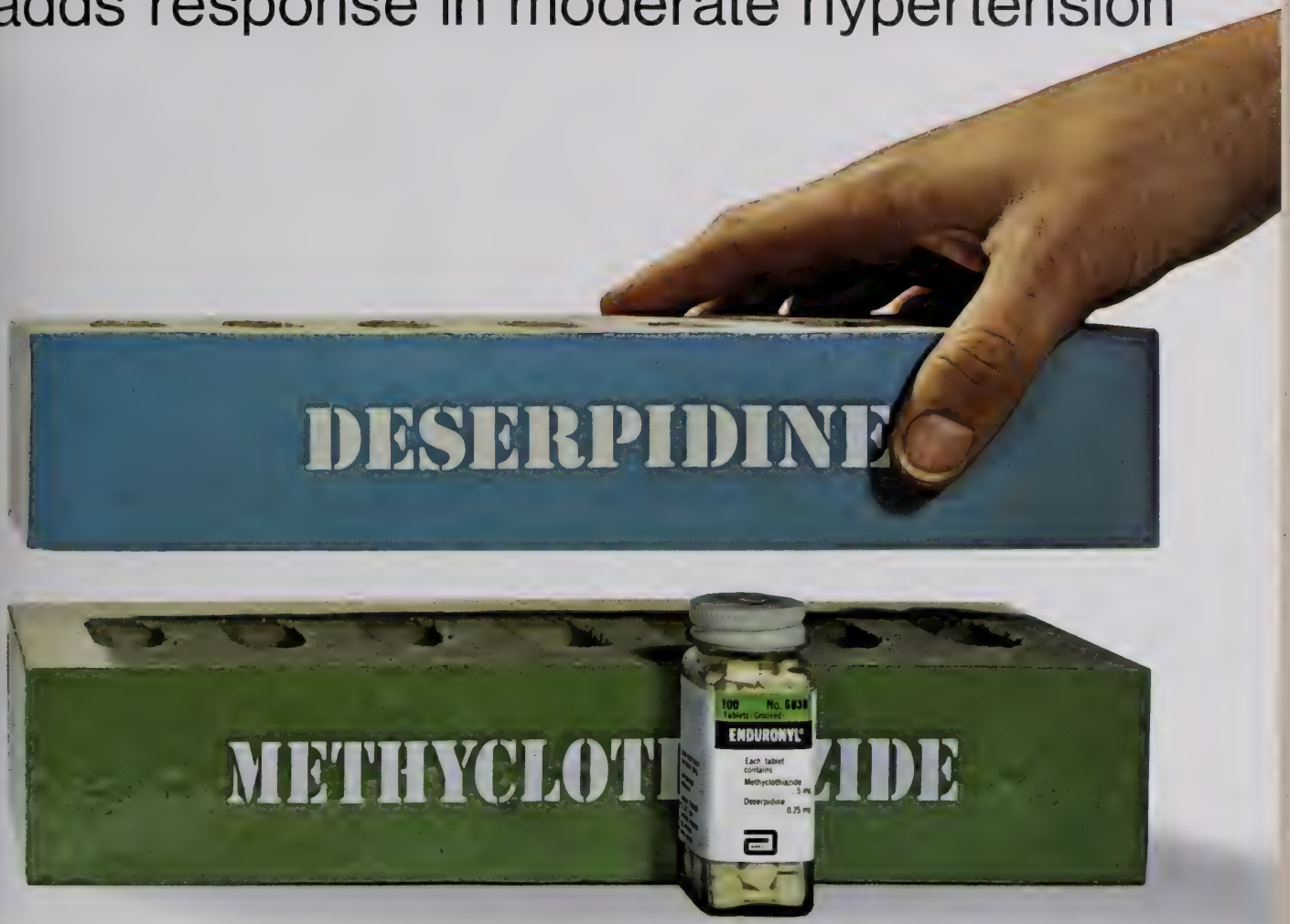
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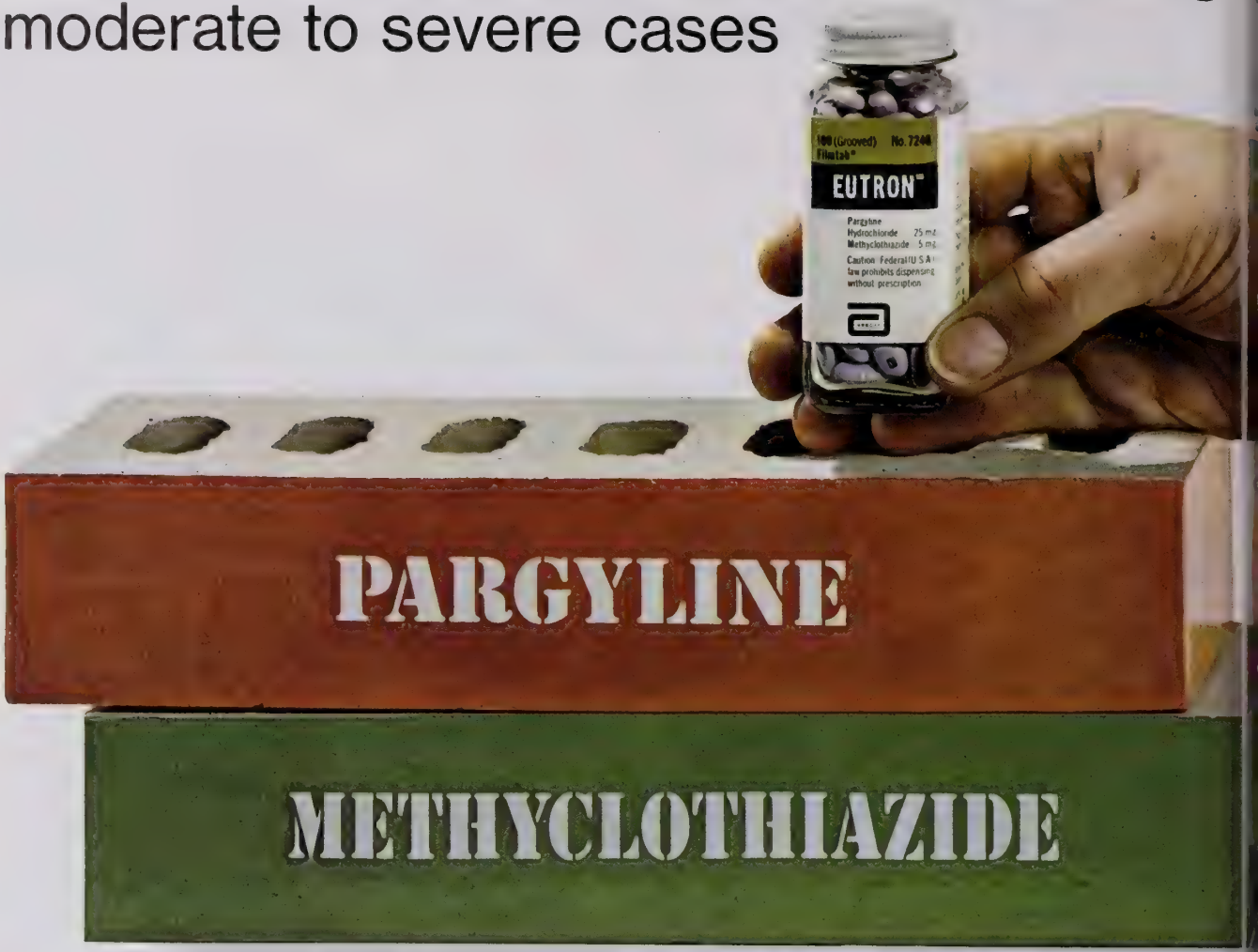
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Deserpidine 0.25 mg. or 0.5 mg

Indications: Edema and mild to moderate hypertension (Enduron), and mild to moderately severe hypertension (Enduronyl). More potent agents, if added, can be given at reduced dosage.

Contraindications: Sensitivity to thiazides; severe renal disease (except nephrosis) or shutdown; severe hepatic disease or impending hepatic coma (hepatic coma due to hypokalemia has been reported in patients on thiazides). Do not use Enduronyl in severe mental depression, suicidal tendencies, active peptic ulcer, or ulcerative colitis.

Warnings: Consider possible sensitivity where there is history of allergy or asthma. If added potassium is indicated, dietary supplementation is recommended. Reserve enteric-coated potassium tablets for cautious use only when necessary, as they may induce serious or fatal small bowel lesions (stenosis with or without ulceration), cause obstruction, hemorrhage, and perforation often requiring surgery; discontinue them immediately if abdominal pain, distention, nausea, vomiting, or g.i. bleeding occurs. Neither Enduron nor Enduronyl contains added potassium.

Precautions: Use thiazides cautiously in severe renal dysfunction, impaired hepatic function or progressive liver disease; also in pregnancy (bone marrow depression, thrombocytopenia, and altered carbohydrate metabolism have been reported in certain newborn). In surgery, thiazides may reduce response to vasopressors, and increase response to tubocurarine. Antihypertensive response may be enhanced following sympathectomy. Watch for electrolyte imbalance (e.g., hyponatremia) in all patients. In hypokalemia (especially in digitalized patients) give supplemental potassium. In hypochloremic alkalosis, give supplemental chloride.

Use rauwolfias with caution in patients with history of peptic ulcer. Rauwolfias with anesthetics may produce hypotension and bradycardia. Discontinue Enduronyl two weeks before elective surgery. Consider vagal blocking agents during emergency surgery. In epilepsy, adjust anticonvulsant dosage. In electroshock, shorten stimulus strength and duration. In occasional patients with depressive tendencies, rauwolfias may precipitate severe mental depression that usually disappears when drug is stopped.

Adverse Reactions: Thiazide reaction include blood dyscrasias (thrombocytopenia with purpura, agranulocytosis, aplastic anemia); elevation of BUN, serum uric acid or blood sugar; anorexia, nausea, vomiting, diarrhea, headache, dizziness, paresthesia, weakness, skin rash, photosensitivity, jaundice, symtomatic gout, and pancreatitis. Cutaneous vasculitis in the elderly has been reported with other thiazides. Adverse effects with deserpidine are qualitatively similar to those with reserpine, but their incidence is lower. These include nasal stuffiness, abdominal cramps or diarrhea, nausea, headache, weight gain, reduced libido and potency, peptic ulcer aggravation, epistaxis, skin eruption, asthma in susceptible patients, electrolyte imbalance, excessive salivation, and reversible Parkinson's syndrome. Excessive drowsiness, fatigue, weakness, and nightmares may signal mental depression. Thrombocytopenia, purpura, and a symptom manifested by dull sensorium, deafness, uveitis, glaucoma, and optic atrophy are rare allergic reactions to other rauwolfias. Hypotension from antihypertensive agents may precipitate angina attacks in susceptible individuals. Usually adverse reactions disappear when drug is withdrawn.

EUTRON™

Each tablet contains
Pargyline Hydrochloride 25 mg.
with Methyclothiazide 5 mg.

Indications: For treatment of patients with moderate to severe hypertension, especially those with severe diastolic hypertension. Not recommended for patients with mild or labile hypertension amendable to therapy with sedatives and/or thiazide diuretics alone. It is desirable to establish the dosage of Eutron by administering component drugs separately.

Contraindications: Pheochromocytoma, advanced renal disease, increasing renal dysfunction, paranoid schizophrenia and hyperthyroidism. Hepatic coma has been reported as consequence of hypokalemia with thiazide therapy. Until further experience is gained not recommended for patients with malignant hypertension, children under 12, or pregnant patients.

Concomitant use of the following is contraindicated: other monoamine oxidase inhibitors; parenteral forms of reserpine or guanethidine; sympathomimetic drugs; foods high in tyramine such as cheese; imipramine and amitriptyline, or similar antidepressants; methyldopa. 2 week interval should separate therapy and use of these agents.

Methyclothiazide is contraindicated in patients with known sensitivity to thiazides.

Warnings: Pargyline hydrochloride is a monoamine oxidase inhibitor. Warn patients against eating cheese, and using alcohol, proprietary drugs or other medication without the knowledge of the physician. When indicated, alcohol, narcotics (meperidine should be avoided), antihistamines, barbiturates, chloral hydrate, and other hypnotics, sedatives, tranquilizers, or caffeine, may be used cautiously in reduced dosage. In emergency surgery ¼ to ⅕ the usual dose of narcotics, analgesics, and other premedications should be used avoiding parenteral administration where possible. Carefully adjust dose of anesthetics to response of patient. Withdraw pargyline two weeks before elective surgery.

Warn patients about the possibility of postural hypotension. Those with angina or coronary artery disease should not increase physical activity with an improvement in well being. Pargyline may lower blood sugar.

Avoid use of enteric-coated potassium tablets, as these may induce serious or fatal small-bowel lesions consisting of stenosis with or without ulceration. These small-bowel lesions have caused obstruction, hemorrhage and perforation frequently requiring surgery. Medication should be discontinued immediately if abdominal pain, distension, nausea, vomiting or GI bleeding occurs. These products contain no added potassium salts and if added potassium intake is desired, dietary supplementation is recommended. Coated potassium tablets should be reserved for cautious use when adequate dietary supplementation is impractical. In patients with a history of allergy or asthma the possibility of sensitivity reactions should be considered.

Precautions: Measure blood pressure while patient is standing to determine antihypertensive effect. Use with caution in hyperactive or hyperexcitable persons. Such persons may show increased restlessness and agitation. Withdraw drug during acute febrile illness. Watch patients with impaired renal function for increasing drug effects or elevation of BUN and other evidence of progressive renal failure; withdraw drug if such alterations persist and progress. Use with caution in patients with liver disease. As with all new drugs, complete blood counts, urinalyses, and liver function tests should be performed periodically. With prolonged therapy, examine patients for change in color perception, visual fields and fundi. Also reported have been: blood dyscrasias including thrombocytopenia with purpura, agranulocytosis and aplastic anemia; elevations of BUN, serum uric acid, or blood sugar. Symptomatic gout may be induced. In surgical patients thiazides may reduce response to vasopressors and increase response to tubocurarine.

Adverse Reactions: Pargyline may be associated with orthostatic hypotension. Mild constipation, slight edema, dry mouth, sweating, increased appetite, arthralgia, nausea and vomiting, headache, insomnia, difficulty in micturition, nightmares, impotence, delayed ejaculation, rash, and purpura have been encountered with pargyline. Hyperexcitability, increased neuromuscular activity (muscle twitching) and other extrapyramidal symptoms have been reported in a few patients with reduced cardiac reserve.

During intensive or prolonged therapy, guard against hypochloremic alkalosis and hypokalemia (especially the latter if patient is on digitalis). Observe all patients for signs of hyponatremia ("low salt" syndrome).

Reported thiazide reactions also include anorexia, nausea, vomiting, diarrhea, headache, dizziness, paresthesia, weakness, skin rash, photosensitivity, jaundice, and pancreatitis. Nocturia has been observed with the combination. 801438

ABBOTT

TM-TRADEMARK

Dislocation of the Jaw

Mochlicus

The jaw-bone is often slightly displaced, and is restored again; it is dislocated but rarely, especially in gaping; in fact, the bone is never dislocated unless it slips while the mouth is opened wide. It slips, however, the more readily from its ligaments being oblique, supple, and of a yielding nature. The symptoms are: the lower jaw protrudes, it is distorted to the side opposite the dislocation, and the patient cannot shut his mouth; when both sides are dislocated, the jaw projects more, the mouth can be less shut, but there is no distortion; this is shown by the rows of teeth in the upper and lower jaw corresponding with one another. If, then, both sides be dislocated, and not immediately reduced, the patient for the most part dies on the tenth day, with symptoms of continued fever, stupor, and coma, for the muscles there induce such effects; there is disorder of the bowels attended with scanty and unmixed dejections; and the vomitings, if any, are of the same character. The other variety is less troublesome. The method of reduction is the same in both: The patient being laid down or seated, the physician is to take hold of his head, and grasping both sides of the jaw-bone with both hands, within and without, he must perform three maneuvers at once,—rectify the position of the jaw, push it backward, and shut the mouth. The treatment should consist of soothing applications, position, and applying a suitable bandage to support the jaw-bone, so as to cooperate with the reduction.—*Hippocrates*

Yellow Fever in Philadelphia in 1793

When yellow fever ravaged the city of Philadelphia in 1793 scenes occurred that were reminiscent of those described by Boccaccio in Florence. A bookseller and publisher, Mathew Carey, gave a vivid account of them:

"The consternation of the people of Philadelphia at this period was carried beyond all bounds. Dismay and affright were visible in almost every person's countenance. Most of those who could by any means make it convenient, fled from the city. Of those who remained, many shut themselves up in their houses, and were afraid to walk the streets. The smoke of tobacco being regarded as a preventative, many persons, even women and small boys, had segars almost constantly in their mouthes. Others placing full confidence in garlic, chewed it almost the whole day; some kept it in their pockets and shoes. . . . Those who ventured abroad, had handkerchiefs or sponges impregnated with vinegar or camphor at their noses, or smelling-bottles full of the thieves' vinegar. Others carried pieces of tarred rope in their hands or pockets, or camphor bags tied round their necks. . . . Many never walked on the foot path, but went into the middle of the streets, to avoid being infected in passing by houses wherein people had died. . . . The old custom of shaking hands fell into such general disuse, that many shrunk back with affright at even the offer of a hand. And many valued themselves highly on the skill and address with which they got to windward of every person whom they met."*

*Henry Sigerist, M.D.: Medicine and Human Welfare, 1941.

No parent should spend all of his time in the garden of a child's life digging up weeds; there is always the danger of scratching out flowers not above the ground.—*Cominco*

Law and Medicine

Compelled Medical Opinion Testimony

BARLOW SMITH, LL.B., M.D.*
Minneapolis, Minnesota

EVERY PERSON has a legal obligation to testify in court to what he has observed in relation to a disputed issue of fact. Thus a physician must give testimony regarding the injuries he observed on the victim of a crime of violence, not because he is an expert in physical examination but solely because he was there to observe.

Courts have the power to punish failure to appear and respond as contempt of court. Here the duty to testify is as a citizen, not as a physician.

The question arises when a physician may be legally compelled to give his medical opinion.

The rule in England was that an expert may not be compelled to give expert opinion testimony in the absence of a contract to do so between him and the party for whom he is to testify**

In the United States most jurisdictions subscribe to one of two general rules: (1) the court cannot compel an expert to testify against his will, and (2) an expert cannot be compelled to testify if he would have to make special study or preparation in order to give his opinion.†

But, when an expert has already performed an examination, he may then be compelled to testify not just to the facts but also to his opinion in jurisdictions following the second rule‡ unless a privilege exists which would require exclusion of the evidence.

For example, it was held in California that a physician hired by a party's attorney to conduct an examination was an agent of the attorney; hence, his report to the latter was privileged under the rule of evidence excluding testimony of communications between attorney and client.§

In such a jurisdiction no different situation exists when the expert is himself a party. Recently an intermediate appellate court in New York ruled that a defendant in a malpractice action may not be compelled to testify even about facts within his knowledge as to proper medical practice and whether

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*New York Bar, the District of Columbia Bar and the Minnesota Bar.

**Webb v. Page, 1 Car. & K. 23(1843).

†Kranshaar Bros. v. Thorpe, 296 N.Y. 223, 72 N.E.2d 165(1947).

‡Neilsen v. Brown, 374 P2d 896(Ore., 1962).

§Porterfield, Right to Subpoena Expert Testimony and Fees Required to be Paid Therefore, 5 Hastings L.J. 50(1953).

his actions deviated therefrom when the question requires his expert opinion.*

In states with discovery procedures for litigants in civil cases, besides being summoned to testify at the trial of a lawsuit, a witness may be summoned to give a deposition. This is an informal meeting of attorneys and witnesses and a person empowered to administer oaths such as a notary public and a stenographer who records questions propounded by the attorneys to the deponent under oath. Failure to appear when subpoenaed for a deposition is punishable as a contempt.

Rule 26 of the Federal Rules of Civil Procedure are very broad: *any* person may be subpoenaed for deposition, not just a party to the lawsuit. However, at least 15 states with rules of procedure modeled after the Federal Rules provide that expert opinion cannot be compelled by deposition. Minnesota Rules of Civil Practice 26.01 makes "any person" subject to subpoena for deposition, but under 26.02 no expert opinion may be required.

Rule 33 pertaining to interrogatories of parties to a lawsuit and Rule 34 pertaining to discovery and production of documents for inspection, copying or photographing make the restrictions of Rule 26.02 applicable to those procedures.**

However, the leading Minnesota case dealing with trial testimony (unrelated to discovery procedures) places no limitation on compelling expert witnesses to give opinion evidence: ". . . I(n) this state no witness can refuse to answer a question on the ground that his answer will be what is known as expert evidence; and this, whether he has been summoned or paid as an expert witness or not."† Inasmuch as this decision was rendered 80 years ago in a murder case and has been only briefly mentioned by the Minnesota Supreme Court in a single subsequent decision, its authority may be ripe for challenge.

*McDermott v. Manhattan Eye, Ear & Throat Hosp., 16 App. Div. 2d 374, 328 N.Y.S. 2d 143(1962).
**2 Youngquist & Blacik, Minnesota Rules Practice.
†State v. Teipner, 36 Minn. 535, 32 N.W. 678(1887).

It's the Law

Pregnancy After Sterilization Operation Is Cause For Suit

The patient, who became pregnant after having undergone a sterilization operation, won an award against the physicians who performed the operation.

The patient had nine children. The physicians told her that having more children would aggravate an existing kidney and bladder condition. They recommended an operation for removal of a portion of the fallopian tubes, which would accomplish sterilization. The patient consented, and the operation was performed. She became pregnant 10 months later.

The patient alleged that the operation failed because of an insufficiency in the procedure. She also claimed that the physician failed to tell her that the operation did not offer complete assurance against becoming pregnant.

The physicians contended that regeneration of the fallopian tubes was out of their hands.

Damages are recoverable for expense of the pregnancy, delivery, and rearing of the child. A California intermediate appellate court ruled in favor of the patient.

Case Reference—Custodio v. Bauer, 59 Cal. Rptr. 463 Cal., May 24, 1967: Rehearing denied, June 13, 1967.
The Citation—15:10, August 12, 1967



Help clear up that miserable stuffed-up feeling with Dimetapp. Each hard-working Extentab brings welcome relief from the stuffiness, drip and congestion of upper respiratory conditions for up to 10-12 hours. Yet, patients seldom experience drowsiness or overstimulation. The key to success is the Dimetapp formula: Dimetane (brompheniramine maleate)—along with phenylephrine and phenylpropanolamine, two time-tested decongestants. They get the job done... in a hurry.

Indications: Dimetapp is indicated for symptomatic relief of the allergic manifestations of respiratory illnesses, such as the common cold and bronchial asthma, seasonal allergies, sinusitis, rhinitis, conjunctivitis, and otitis.
Contraindications: Hypersensitivity to antihistamines. Not recommended for use during pregnancy.
Precautions: Until patient's response has been determined, he should be cautioned against engaging in operations requiring alertness. Administer with care to patients with cardiac or peripheral vascular diseases or hypertension.
Side Effects: Hypersensitivity reactions including skin rashes, urticaria, hypotension and thrombocytopenia, have been reported on rare occasions. Drowsiness, lassitude, nausea, giddiness, dryness of the mouth, mydriasis, increased irritability or excitement may be encountered.
Dosage: 1 Extentab morning and evening.
Supplied: Bottles of 100 and 500.

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Dimetapp® Extentabs®
(Dimetane® [brompheniramine maleate], 12 mg.; phenylephrine HCl, 15 mg.; phenylpropanolamine HCl, 15 mg.)
up to 10-12 hours clear breathing on one tablet



If hypothyroidism leaves your patient feeling like this...

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Synthetic Thyroid Replacement Therapy



Letter® provides all the advantages of the synthetically pure chemical sodium levothyroxine. Dosage is precise and potency is consistently uniform.

and

Letter® is micronized to provide maximum opportunity for full absorption and clinical response.

In addition Letter® is distinctively color coded with an identifying number stamped on each tablet to provide accurate dosage control.

Indications: Hypothyroid conditions. **Contraindications:** Thyrotoxicosis, acute myocardial infarctions unless associated with hypothyroidism. In hypothyroidism with hypoadrenalism coadministration of corticoids with LETTER® is recommended. **Precautions and Side Effects:** Excessive dosage may result in diarrhea, cramps, palpitation, nervousness, rapid pulse, sweating. If symptoms appear, discontinue medication for several days, then reinstitute at a lower level. Since myxedema patients with heart disease may suffer seriously from abrupt increases in dosage, caution should be exercised in adjusting dosage. **Dosage:** Generally, the initial adult dosage is 0.1 mg. daily. This may be increased in small increments every one to three weeks until proper metabolic balance is achieved. **Available:** Bottles of 100 tablets, in six potencies: 0.025 mg. (violet), 0.05 mg. (peach), 0.1 mg. (pink), 0.2 mg. (green), 0.3 mg. (yellow), and 0.5 mg. (white).

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Abstracts, Briefs and Commentaries

GASTROINTESTINAL FUNCTION FOLLOWING VAGOTOMY AND PYLOROPLASTY

The authors reviewed 45 cases (eight patients with gastric ulcer and 37 with duodenal ulcer). The surgical procedure was total abdominal vagotomy and a Mikulicz pyloroplasty. The authors evaluated postoperative posture, peristalsis, and subsequent intestinal absorption of xylose.

Appropriate positioning (right lateral position) after operation results in adequate emptying during the adynamic phase of gastric function. This is begun immediately.

In as early as six hours the stomach empties, and intestinal motility and absorption are unimpaired. The absence of bowel sounds does not mean absence of peristalsis and is of no diagnostic value.

Routine gastric decompensation may be unnecessary. Perhaps a more generous attitude of oral intake might be feasible.

Jerome T. Grismer, M.D.
Minneapolis, Minnesota

Argyropoulos, G. D., White, M. E. E.: Arch Surg 93:578, 1966.

TUMORS OF THE PAROTID GLAND

During an 18-year period 153 cases of parotid tumors were seen at the M. D. Anderson Hospital, 42 benign and 111 malignant. Superficial lobectomy was done on all patients either to remove the tumor in its entirety or to get at the deeper lobe. Recommendation is made for inclusion of the first echelon of nodes (parotid and jugulodigastric) with the specimen. A simultaneous neck dissection is made with clinically positive nodes in cases where malignancies are discovered. Irradiation is given where residual or suspected tumor remains at the margins of resection.

Of the patients with a malignant tumor 53% were living and free of disease five years after surgery. However, only four of the 21 patients with histologically proven cervical metastases survived five years. Facial paralysis was an ominous sign when present prior to surgery. Eight of nine patients with this sign were dead as a result of their disease within 24 months. Only two of the 42 benign cases treated developed a recurrence.

Harrison H. Farley, M.D.
Minneapolis, Minnesota

Bardwel, John.: Tumors of the Parotid Gland. Amer J Surg 114:4:498, 1967.

MASSIVE UPPER GASTROINTESTINAL HEMORRHAGE DUE TO PANCREATITIS

Massive hemorrhage is most likely due to erosion of a large retroperitoneal vessel. Minor hemorrhage may result from gastritis, peptic ulcer, or varices. Two cases are presented.

The salient features of this syndrome are massive recurrent hemorrhage (melena), vomiting, and nonresponse to either medical or surgical treatment. Bleeding points may not be found at exploration. The serum amylase may not be elevated. There is no experience of ligation of large vessels in the necrotic pancreas. This complication occurs rather frequently in acute pancreatitis.

The physician should be suspicious of acute hemorrhagic pancreatitis in all instances of massive gastrointestinal bleeding.

Comment: The author is aware of a patient who, subsequent to pancreatitis, developed massive recurrent gastric hemorrhage. This was not helped by either medical or surgical treatment until successful ligation of an eroded artery in the gastric fundus.

Jerome T. Grismer, M.D.
Minneapolis, Minnesota

Haller, J. D., Pena, C., Dargan, E. L.: Arch Surg 93:567, 1966.

CEREBRAL CREATINE PHOSPHOKINASE

These days serum creatine phosphokinase is getting a big play in clinical laboratories. The reasons for this are obvious. Heart muscle and skeletal muscle contain most of the creatine phosphokinase in the body, while the liver has none. This happy state of distribution allows clinicians to distinguish which organ is in trouble. But it turns out that things aren't that clear-cut. A group of Englishmen from Newcastle General Hospital now tell us that about 15 of 21 patients with cerebral damage from head injuries, acute cerebrovascular accidents, and meningitis had high serum creatine phosphokinases. Which makes sense, for although the heart and skeletal muscle have most of the enzyme, the brain also contains generous amounts. But, and here is the catch, when the serum enzyme of these patients was fractionated, it was largely from muscle. As the authors say, "Why muscle-C.K. is often much increased in the serum in such cases remains unclear."

Richard L. Reece, M.D.
Minneapolis, Minnesota

Dubo, H., Park, D. C., Pennington, R. J. T., Kalbag, R. M., and Walton, J. N. The Lancet, 2:743, 1967.

ALTERED LYMPHATIC DYNAMICS CAUSED BY CANCER METASTASES

Changes in lymphatic dynamics subsequent to metastases in the lymphatic vessels or nodes will alter the subsequent plan of treatment for cancer.

The normal lymphatic compartmental systems of the upper and lower extremity are described. There are numerous lymphatic-venous connections.

When blocked by neoplasm, the lymphatic flow may shift to other compartments. Awareness of this will allow proper surgical therapy. Often the bizarre lymphatic networks will completely bypass lymph nodes. The level or location of the block determines the nature of the collateral systems. The perivascular and perineural lymphatics may allow transport over great

distances. Dissemination of neoplasm via the lymphicovenous anastomoses probably occurs. Satellitosis (satellite dermal metastases as in melanoma) result from expansive dermal lymphatics secondary to major lymphatic obstruction.

Jerome T. Grismer, M.D.
Minneapolis, Minnesota

Ariel, I. M., Resnick, M. I.: Altered Lymphatic Dynamics Caused by Cancer Metastases. Arch Surg 94:117, 1967.

NOW COFFEE

Man's habits, if overdone, sometimes produce unexpected diagnostic problems. Too many artificially sweetened soft drinks, for example, can cause a skin rash to erupt when the patient is exposed to light. And too many cigarettes can, among other things, lead to eosinophilia. Coffee? Well, coffee, when taken to excess, can produce a low grade irregular fever.[3] Doctor Hebart Reimann, in a recent JAMA article, tells the story of a 39-year-old housewife who for six months had a fever of 99 to 100.4, was unable to eat or sleep, became irritable, and lost 20 pounds. When she entered the hospital, her fever stopped. Doctor Reimann questioned her and found she drank 15 to 18 cups of coffee a day. When coffee was restricted, her temperature stayed normal, her appetite improved, her insomnia abated, and she gained five pounds.

Richard L. Reece, M.D.
Minneapolis, Minnesota

References

1. Lamberg, S. I.: A New Photosensitizer. JAMA 201:747, 1967.
2. Schoen, I., and Pizer, M.: Eosinophilia Apparently Related to Cigarette Smoking. New Engl J Med 270:1344, 1964.
3. Reimann, H. A.: Caffeinism. JAMA 202:1105, 1967.

NODOSA OR NOT NODOSA

Given a patient with migrating pulmonary infiltrates and persistent eosinophilia, what diagnosis should a physician consider—periarteritis nodosa or Loeffler's pneumonia? According to recent articles,[1,2] both are possibilities. Drs. Kinsella and Simpson of Springfield, Massachusetts, report a 61-year-old woman who, four years after a bout of "Loeffler's pneumonia," died of generalized vasculitis.[1] In 1965, Drs. Dines and Donoghue of the Mayo Clinic observed two patients, a 46-year-old farmer and a 34-year-old farmer's wife, with lung infiltrate and with 50 and 31 percent eosinophils respectively.[2] Both responded promptly to steroids, and the Mayo physicians diagnosed Loeffler's syndrome instead of periarteritis nodosa. How does one differentiate the two diseases? In periarteritis, long symptoms last longer, and patients are more likely to be anemic, to have renal disease, to cough up blood, to show pleural effusions, and to develop other problems that go with multisystem disease. When none of these signs or symptoms are present, time tells.

Richard L. Reece, M.D.
Minneapolis, Minnesota

References

1. Kinsella, D. L., and Simpson, H. N.: Loeffler's Pneumonia Terminating in Fatal Periarteritis Nodosa, JAMA 202:867, 1967.
2. Dines, D. E., Donoghue, F. E., Loeffler's Syndrome, JAMA 192:254, 1965.

What you take in is determined by what you put out.—*Forbes Epigrams*



She doesn't feel she "suffers" from hypertension

Butiserpazide® lowers blood pressure so smoothly that patients are often untroubled by either disease *or* therapy

By switching patients to BUTISERPAZIDE you may be able to free them of much of the burden of hypertension. Clinical comparisons have shown that many respond with (1) smooth, uniform lowering of blood pressure[1]...at times to levels *below* those attained with previous therapy[2]; (2) "striking" improvement in such symptoms as headache, nervousness, palpitation and dizziness[2]; plus (3) "...lowered incidence of drug side effects."[2]

And there's an added advantage: the usual dosage is just 1 tablet once or twice daily, often without need for supplementary therapy. (BUTISERPAZIDE provides not only hypotensive and diuretic action, but a mildly sedative effect as well.) Isn't this the way to take the suffering out of hypertension?

You have a choice of 2 strengths:

Butiserpazide®-25
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BUTISOL® (butabarbital) 30 mg. (½ gr.)†;
Hydrochlorothiazide 25 mg. (⅜ gr.); Reserpine 0.1 mg.

in mild to moderate cases, often effective at half the usual thiazide or thiazide/reserpine dosage.

Butiserpazide®-50
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Hydrochlorothiazide 50 mg. (¾ gr.); Reserpine 0.1 mg.

controls many moderate to severe cases without any need for ganglionic blockers, or other more potent agents; if such agents are needed, their dosage can be cut in half.

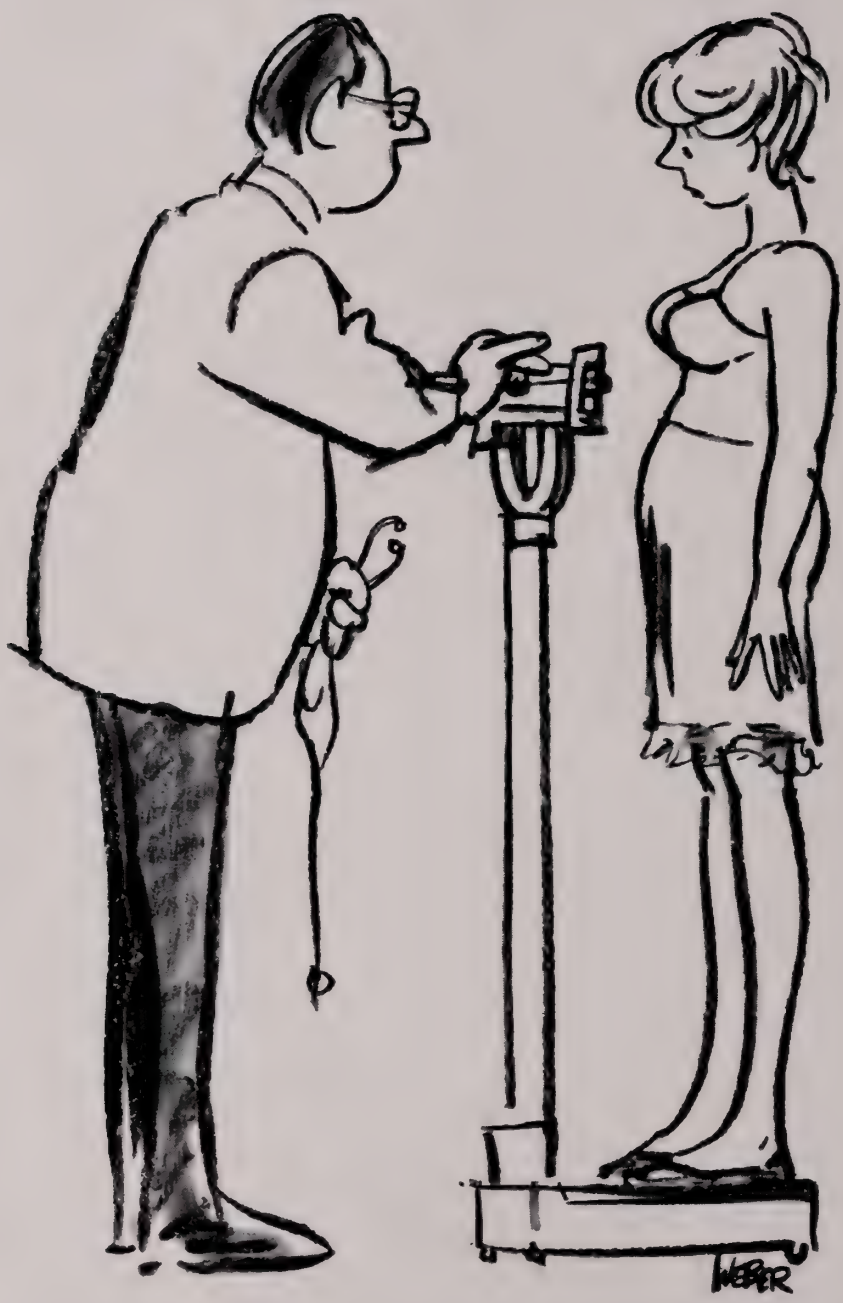
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*15 mg. of **Butisol** (butabarbital), plus the other ingredients, in outer layer; 15 mg. of **Butisol** (butabarbital) in a specially coated core for delayed action, to approximately equalize duration of action for all components.

Contraindicated in presence of renal impairment, peptic ulcer, ulcerative colitis, or mental depression, and in patients with porphyria or those sensitive to any component. **Warning:** Coated potassium tablets, sometimes administered in conjunction with antihypertensive therapy, may be associated with small bowel lesions which have led to obstruction hemorrhage, and perforation. Surgery has been required and deaths have occurred. Such tablets should be used only when indicated and when adequate dietary supplementation is not practical. They should be discontinued immediately if abdominal pain, distention, nausea, vomiting or gastrointestinal bleeding occur. **Precautions:** Exercise caution in hepatic disease, diabetes, surgery, coronary artery disease, epilepsy, E.S.T., and in patients receiving digitalis. **Side Effects:** Electrolyte imbalance, hyponatremia, hypochloremic alkalosis and/or hypokalemia, hyperuricemia and gout, bradycardia, drowsiness, skin rashes, hangover, systemic disturbances, weakness, leg cramps, diarrhea, epistaxis, dizziness, urticaria, dry itching skin, nausea, vomiting, palpitation, superficial skin bruises, headache, dehydration, paresthesias, photosensitivity, pancreatitis, jaundice, xanthopsia, thrombocytopenia, leukopenia, agranulocytosis, aplastic anemia, nasal congestion, hypotension, lassitude, loose stools, anorexia, bizarre dreams, peptic ulcer, ulcerative colitis, mental depression. (Ammonium chloride, which may be administered to reverse hypochloremic alkalosis, should not be given to patients with hepatic disease.) **Before prescribing or administering, see package insert.** †**Warning:** May be habit forming. **Usual Adult Dosage:** Butiserpazide®-25 or Butiserpazide®-50: 1 tablet daily or b.i.d. **References:** 1. Johnson, H. J., Jr.: Penna. M. J.: **67**:35, 1964. 2. Coodley, E. L.: Curr. Ther. Res. **4**:460, 1962.

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Get them while they're easily reversible.

Obesity doesn't happen suddenly. This insidious process has its beginning—and the chances of reversing it are better—during the *first 10 to 15 pounds of weight gain.* When a new dietary pattern must be established, consider the adjunctive use of BAMADEX SEQUELS. Combining the proven *anorexigenic* action of d-amphetamine with the *tranquilizing* effect of meprobamate, BAMADEX SEQUELS controls appetite throughout the day, usually with a single capsule daily.

Contraindications: Dextro-amphetamine sulfate: In hyperexcitability and in agitated prepsychotic states. Previous allergic or idiosyncratic reactions to meprobamate.
Precautions: Use with caution in patients hypersensitive to sympathomimetic compounds, who have coronary or cardiovascular disease, or are severely hypertensive.

Dextro-amphetamine sulfate: Excessive use by unstable individuals may result in psychological dependence.

Meprobamate: Careful supervision of dose and amounts prescribed is advised, especially for patients with known propensity for taking excessive quantities of drugs. Excessive and prolonged use in susceptible persons, e.g. alcoholics, former addicts, and other severe psychoneurotics, has been reported to result in dependence on the drug. Where excessive dosage has continued for weeks or months, reduce dosage gradually. Sudden withdrawal may precipitate recurrence of preexisting symptoms such as anxiety, anorexia, or insomnia; or withdrawal reactions such as vomiting, ataxia, tremors, muscle twitching and, rarely, epileptiform seizures. Should meprobamate cause drowsiness or visual disturbances, reduce dosage and avoid operation of motor vehicles, machinery or other activity requiring alertness. Effects of excessive alcohol consumption may be increased by meprobamate. Appropriate caution is recommended with patients prone to excessive drinking. In patients prone to both petit and grand mal epilepsy meprobamate may precipitate grand mal attacks. Prescribe cautiously and in small quantities to patients with suicidal tendencies.
Side Effects: Overstimulation of the central nervous system, jitteriness and insomnia or drowsiness. Dextro-amphetamine sulfate: Insomnia, excitability, and increased motor activity are common and ordinarily mild side effects. Confusion, anxiety, aggressiveness, increased libido, and hallucinations have also been observed, especially in mentally ill patients. Rebound fatigue and depression may follow central stimulation. Other effects may include dry mouth, anorexia, nausea, vomiting, diarrhea, and increased cardiovascular reactivity.

Meprobamate: Drowsiness may occur and can be associated with ataxia; the symptom can usually be controlled by decreasing the dose, or by concomitant administration of central stimulants. Allergic or idiosyncratic reactions: maculopapular rash, acute nonthrombocytopenic purpura with petechiae, ecchymoses, peripheral edema and fever, transient leukopenia. A case of fatal bullous dermatitis, following administration of meprobamate and prednisolone, has been reported. Hypersensitivity has produced fever, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, stomatitis, proctitis (1 case), anaphylaxis, agranulocytosis and thrombocytopenic purpura, and a fatal instance of aplastic anemia, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity, usually after excessive dosage. Impairment of visual accommodation. Massive overdosage may produce drowsiness, lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse.

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Popular Fallacies

Medical Folklore Usually Wrong

While much of medical folklore is now obsolete and largely forgotten, there are still many completely erroneous beliefs about their health held by sizeable numbers of people in our so-called age of enlightenment.

Today's Health Guide, the American Medical Association's manual of health information for the American family, points out that grandma is not always wrong in her concepts of health. But she often is wrong.

The book lists some of the common misconceptions about health—

- Eating between meals is always harmful (untrue).
- Bad breath means disease (not so).
- Milk should not be taken at the same time as sour fruits (not so).
- Proteins and carbohydrates should not be eaten at the same meal (incorrect).
- Daily bowel movements are necessary for health (untrue).
- Pain in the back must indicate kidney disease (incorrect).
- Pain in the abdomen means an overloaded stomach (wrong).
- A laxative is good for abdominal pain (it is sometimes dangerous).
- Food kept in an open tin can is necessarily poisonous (not if properly refrigerated).
- Scales from scarlet fever and measles spread the disease (nose and throat secretions actually do).
- Sewer gas makes people sick (no—it's just unpleasant).
- Pimples and boils indicate bad blood (they are due to infections).
- Boric acid strengthens the eyes (it does not).
- Fried and highly seasoned foods are harmful (not in moderation).
- A cold can be broken up or cured (it cannot).
- You feed a cold and starve a fever (no).
- Eye muscle exercises will eliminate the need for glasses (a dangerous fallacy).
- Vegetarianism is good for health (it simply makes good nutrition more difficult).

Medical Men On Postage Stamps

Franz Donders (1818-1889), Dutch ophthalmologist, who studied conveyance of axes and accommodation, regeneration of cornea, hypermetropia, ametropia, and astigmatism, is credited with the discovery of clinical refraction and with the introduction of prismatic and cylindrical lenses for eyeglasses. A 1935 Netherlands postage stamp commemorates his notable achievements.

Theodor Bilharz (1825-1862), was a German physician and researcher in tropical diseases, particularly bilharziasis. In his capacity as helminthologist he identified the cause of certain endemic blood disorders as a trematode worm subsequently designated Bilharzia after its discoverer. In recognition and appreciation the United Arab Republic honored Bilharz on a postage stamp issued in 1962.

When death comes to me it will find me busy unless I am asleep. If I thought I was going to die tomorrow, I should nevertheless plant a tree today.—*Stephen Crane*



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Turn page for contraindicati precautions and side effects.

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Contraindications: Tuberculous, fungal, and most viral lesions of the skin (including herpes simplex, vaccinia, and varicella). Not for ophthalmic use. Contraindicated in individuals with a history of hypersensitivity to any of the components. *Precautions:* Synalar preparations are virtually nonsensitizing and nonirritating. However, the solution may produce burning or stinging when applied to denuded or fissured areas. In some patients with dry lesions, the solution may increase dryness, scaling or itching. Where severe local infection or systemic infection exists, the use of systemic antibiotics should be considered, based on susceptibility testing. While topical steroids have not been reported to have an adverse effect on pregnancy, the safety of their use on pregnant females has not absolutely been established. Therefore, they should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time. *Side Effects:* Side effects are uncommon with topical corticosteroids. As with all drugs, however, a few patients may react unfavorably to Synalar under certain conditions. In such cases the agent should be discontinued and appropriate measures taken. *Availability:* Synalar (fluocinolone acetonide) Cream 0.025%—5, 15 and 60 Gm. tubes and 425 Gm. jars. Cream 0.01%—15, 45 and 60 Gm. tubes and 120 Gm. jars. Solution 0.01%—20 and 60 cc. plastic squeeze bottles. Ointment 0.025%—15 and 60 Gm. tubes. Neo-Synalar® (neomycin sulfate 0.5% [0.35% neomycin base], fluocinolone acetonide 0.025%) Cream—5, 15 and 60 Gm. tubes.

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Book Reviews

The problem of education is twofold: first to know, and then to utter. Everyone who lives any semblance of inner life thinks more nobly and profoundly than he speaks.—R. L. Stevenson

DIAGNOSTIC PROCEDURES IN GASTROENTEROLOGY—By Charles H. Brown, M.D. 438 pages, $19.00. The C. V. Mosby Company, St. Louis.

This monograph dealing with various phases of gastroenterology is divided into eight parts and is written by physicians from the Cleveland Clinic Foundation as a manual for the physician who wishes to increase his diagnostic ability and determine the variety of procedures that are carried out in the study of gastrointestinal diseases. It covers the medical as well as the surgical phases of this problem.

The minute details of technique are not enumerated and for that reason the book has more value to the individual who has already been initiated into the clinical phases of gastroenterology. For the student in the medical school or entering into his specialty, the details of technique are insufficient and it would be expected that other monographs should be used for that purpose.

A great many diagnostic hints and suggestions are provided and it was interesting to note that the patient who presents with multiple abdominal scars very often may be suffering from a conversion neurosis unless organic evidence of specific disease can be identified.

Supplemental instructions for the patient and supplementary diets are appended to the last hundred pages.

Carl O. Rice, M.D.
Minneapolis, Minnesota

GYNECOLOGIC PATHOLOGY — Frederick T. Kraus, 504 pages, The C. V. Mosby Company: St. Louis, $18.50, 1967.

Dr. Kraus, Associate Pathologist at St. Lukes Hospital in St. Louis and Instructor in Pathology at Washington University School in Medicine, has assembled a sound book. He systematically covers his subject, illustrates lesions with excellent drawings and photographs, and adds an extensive list of recent references.

Although this volume has the credentials of a good textbook, I have reservations about it. It adds little, for instance, to such books as *Novak's Gynecological and Obstetrical Pathology.* Also I find the prose a little wooden. The author plods down well-worn paths, uses the standard descriptive approaches, and writes with carefully hedged long sentences in the passive voice. Though the style is stereotyped, I cannot quibble with the substance. The facts are there, and they are well-organized, clear, and correct.

Richard L. Reece, M.D.
Minneapolis, Minnesota

WILBUR J. COHEN: The Pursuit of Power—Marjorie Shearon. Shearon Legislative Service, Chevy Chase, Maryland, 240 pages, $4.50.

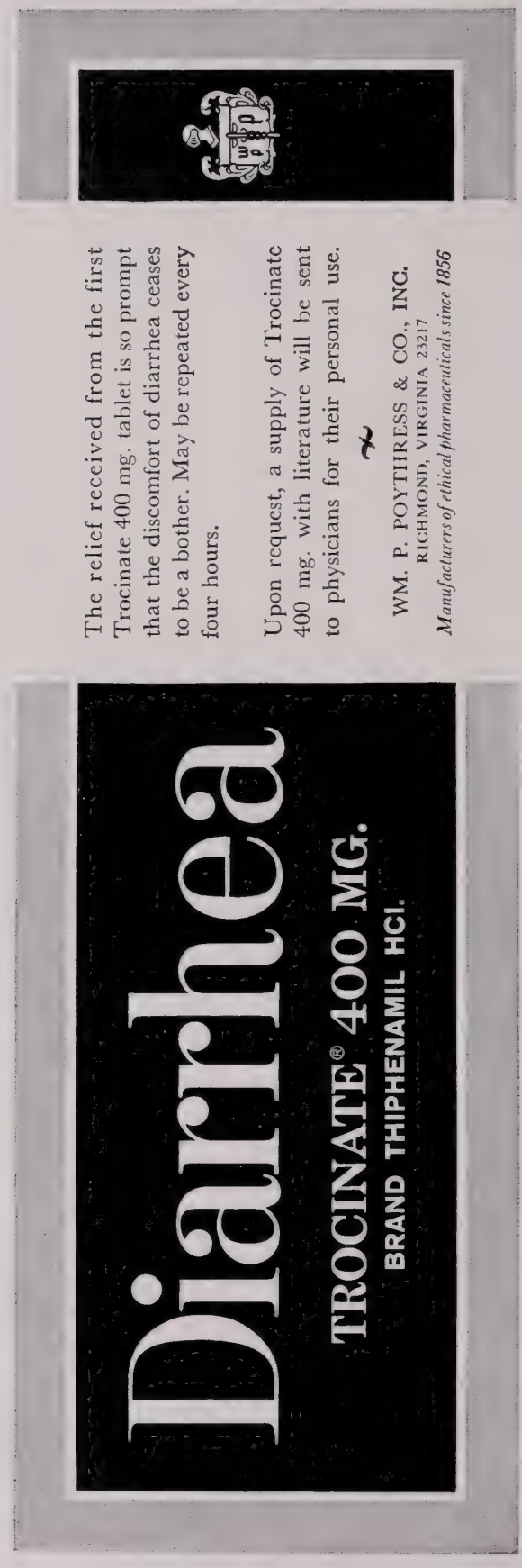
This is an almost incredible account of political chicanery. If I had not read "Mein Kampf" and lived through World War II, I would find a very wide "credibility gap" between myself and Mrs. Shearon. As it is, I am inclined to believe most of what she has set forth in such great detail, not because I am a physician supporting most of the A.M.A. policies, or of the same political persuasion as Mrs. Shearon, but because she has developed this story of intrigue in such a careful manner.

It would be sheer folly for anyone to put into print the accusations and insinuations which she has presented in her charges not only against Wilbur J. Cohen, the main villain in her book, but against many others who are still on the living, breathing list. She talks at some length about the White House Conference on Aging, held in January, 1961. As a member of Governor Anderson's State Council on Aging, I happened to be invited to attend a follow-up of this conference.

Three of us, two staunch Democrats and myself, attended this meeting, where I had the privilege of attending several workshops with a man who was to become one of the best known physicians in these United States, Dr. Edward Annis of Miami, Florida. I give this personal background because I want to say that my own experiences at this meeting make her tale very credible. It was one of those "stacked" meetings, but not so much so that the collective physicians' voices could not be heard. We succeeded in "torpedoing" this meeting, as far as the HEW people were concerned, because we insisted that the truth be told about the subjects under discussion!

THE PURSUIT OF POWER is not as exciting a book to read as WITNESS, by Whittaker Chambers, but comes close and should be MUST reading for every American who is worried about the future of this country of ours. If you aren't concerned before you read this book, you will be afterwards; because the time Mrs. Shearon talks about is NOW!

Charles G. Sheppard, M.D.
St. Peter, Minnesota



Classified

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WANTED: General practitioner, to join two G.P.'s well established in north central Minnesota community, 2200 pop., 65 miles from Twin Cities. Excellent office space with lab and X-ray, just opened new hospital, all facilities. Assistantship or partnership. Considerable surgery and obstetrics. Hunting, fishing, golf club. Great opening for interested G.P. WRITE MINNESOTA MEDICINE—381; 375 Jackson, St. Paul, 55101.

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PSYCHIATRIC RESIDENCIES: Approved three-year progressive program in Metropolitan Detroit area. University associations. Teaching staff of Board men, psychoanalysts, professors, outstanding visiting lecturers. Active Research. Modern physical plant. Salary $8,978; $9,405; $10,213. Five year career program $10,213 to $18,507. 10% increase expected in July. Liberal Civil Service benefits. General Practitioners completed internship four years ago may be eligible for NIMH stipends of $12,000 per year. Write, Director of Education and Research, Northville State Hospital, Northville, Michigan 48167.

GENERAL PRACTITIONER with 25 years experience and a well-established practice in a suburb of the city desires a General Practitioner with an association towards a partnership. Write: MINNESOTA MEDICINE-389, 375 Jackson, St. Paul 55101.

Classified Advertisements

PHYSICIAN WANTED: G.P. with additional surgical and OB experience—desired to associate with two G.P.'s with similar experience in large, well established practice in Central Minnesota. Hospital accredited, 300 bed, open staff, complete services. Salary leading to partnership. Adequate housing in area. Send background information, professional and personal to: Dr. Goehrs, 825 First Street North, St. Cloud.

THREE MAN group in North West Wisconsin Resort, State Conservation and Retirement Area needs two more physicians adequately to serve their practice. Facilities offered are three-room physician suites, X-ray and lab under AMT technician, RN-only nursing personnel. New accredited thirty-two bed hospital and forty-six bed nursing home. Deer and duck hunting, fishing within five minutes of town. Internist most needed; generalists welcomed. Will meet any reasonable salary request. Partnership after one year. Write: MINNESOTA MEDICINE—365; 375 Jackson St., St. Paul 55101.

TWO MAN PARTNERSHIP desires a third in general practice. Good office set-up in growing industrial town of 15,000 in Southern Minnesota. Excellent hospital, school systems and recreational facilities. One hour on freeway to downtown Minneapolis. Contact: Drs. Floersch & McEnaney, 127 West Vine Street, Owatonna, Minnesota 55060.

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WANTED: YOUNG PHYSICIAN for association leading to partnership with four well-established General Practitioners in fast-growing suburb of St. Paul. Excellent clinic facilities in nearly new, partnership owned, well equipped, medical center building. Contact: A. Eugene Muller, M.D., North St. Paul Medical Center, 2579 East 7th Avenue, North St. Paul, Minnesota 55109.

GENERAL PRACTITIONER wanted to join well established practitioner in city of 5-6,000 and serving a population area of 18-20,000. Approximately 75 miles west of Mpls.-St. Paul. Well-kept clinic building two blocks from the hospital. Fully accredited 80 bed hospital with a resident Pathologist, Radiological Service, LPN School, X-ray Technician School, and complete Physiotherapy Department. Short-term association on salary basis or long-term association with eventual partnership, will accept, consider and appreciate either terms. Please send short resume of your education and previous experience. For further information about this opportunity write: Gregory M. Olson, M.D., Litchfield, Minnesota 55355.

WANTED—YOUNG INTERNIST. Board certified or eligible, to join 8-man group consisting of 6 GP's, a general surgeon, and a radiologist; college town of 5500 only 30 miles from Twin Cities; salary negotiable with early partnership opportunity. Write or call collect: Ed Jenkins, Mgr., River Falls Medical Clinic, River Falls, Wisconsin, phone 425-5322.

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WANTED—YOUNG GP, to join 8-man group of 6 GP's, a general surgeon, and a radiologist; college town of 5500 only 30 miles from Twin Cities; salary negotiable with early partnership opportunity. Write or call collect: Ed Jenkins, Mgr., River Falls Medical Clinic, River Falls, Wisconsin. Phone 425-5322.

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PSYCHIATRISTS, PEDIATRICIANS, internists, physicians—join staff of treatment facility for retarded children and adults located 45 miles from Minneapolis-St. Paul area. Contact: E. J. Engberg, M.D., Superintendent, Faribault State Hospital, Faribault, Minnesota 55021.

GENERALIST as member of Medical Staff of progressive State Hospital in Michigan's vacationland. Hospital has 3-year accreditation, JCAH and 3-year residency accreditation by A.P.A. Salary $16,000 to $19,800. Excellent fringe benefits. Civil Service security when qualified. Apply L. B. Young, M.D., Director of Medical Services, Traverse City State Hospital, Traverse City, Michigan 49684.

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Minnesota Medicine Cover Photographs

In order to encourage more physicians to submit color slides for use on the cover of MINNESOTA MEDICINE the competition is being discontinued. The picture editor now invites all physician-photographers to send 35 mm. color slides of suitable subjects for consideration as cover pictures. The format must be horizontal because of printing limitations. Pictures high-lighting Minnesota seasons, places, and activities will have an automatic advantage. No limit as to the number of slides sent will be set, but all slides should be individually identified. All slides will be returned. Physicians whose pictures are used as covers will be recognized in MINNESOTA MEDICINE. We can use many more pictures than we have received in the past.

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DECLOMYCIN Demethylchlortetracycline should be equally or more effective therapeutically than other tetracyclines when the offending organisms are tetracycline-sensitive.

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Warning—In renal impairment, usual doses may lead to excessive accumulation and liver toxicity. Under such conditions, lower than usual doses are indicated, and, if therapy is prolonged, serum level determinations may be advisable. A photodynamic reaction to natural or artificial sunlight has been observed. Small amounts of drug and short exposure may produce an exaggerated sunburn reaction which may range from erythema to severe skin manifestations. In a smaller proportion, photoallergic reactions have been reported. Patients should avoid direct exposure to sunlight and discontinue drug at the first evidence of skin discomfort. Necessary subsequent courses of treatment with tetracyclines should be carefully observed.

Precautions—Overgrowth of nonsusceptible organisms may occure. Constant observation is essential. If new infections appear, appropriate measures should be taken. In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment.

Side Effects—Gastrointestinal system—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin—maculopapular and erythematous rashes. A rare case of exfoliative dermatitis has been reported. Photosensitivity; onycholysis and discoloration of the nails (rare). Kidney—rise in BUN, apparently dose related. Transient increase in urinary output, sometimes accompanied by thirst (rare). Hypersensitivity reactions—urticaria, angioneurotic edema, anaphylaxis. Teeth— dental staining (yellow-brown) in children of mothers given this drug during the latter half of pregnancy, and in children given the drug during the neonatal period, infancy and early childhood. Enamel hypoplasia has been seen in a few children. If adverse reaction or idiosyncrasy occurs discontinue medication and institute appropriate therapy.

Average Adult Daily Dosage: 150 mg q.i.d. or 300 mg b.i.d. Should be given 1 hour before or 2 hours after meals, since absorption is impaired by the concomitant administration of high calcium content drugs, foods and some dairy products. Treatment of streptococcal infections should continue for 10 days, even though symptoms have subsided.

In the treatment of syphilis a dosage schedule of a total of 12 to 18 Gm. given in equally divided doses over a period of 10 to 15 days should be followed. Close follow-up observation of the patient is recommended, including appropriate laboratory tests, since demethylchlortetracycline has not had adequate evaluation in all stages of syphilis. Spinal fluid examination should be included as part of this follow-up.

Acute gonococcal anterior urethritis in males has been treated effectively with a single dose of 600-900 mg. of DECLOMYCIN Demethylchlortetracycline. Individuals unable to tolerate large single doses due to gastrointestinal side effects may be treated with 150 mg. every 6 hours for a minimum of 4 doses or 300 mg. every 12 hours for a minimum of 2 doses. Females should be treated with a dosage of 150 mg. every 6 hours or 300 mg. every 12 hours until a cure is effected.

Primary Atypical Pneumonia (Eaton Agent): The average adult daily dosage is 900 mg. in 3 divided doses for six days.

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Special Article

Analysis of Appendectomies in Duluth

ROBERT J. CAMPAIGNE, M.D.*
Duluth, Minnesota

SINCE THE CLINICIAN Reginald Fitz of Boston coined the term appendicitis in 1886[1] and appendicitis was listed on the vital statistics as a cause of death in 1892,[2] the disease entity has reached paramount importance as a diagnostic probability. The inflamed appendix remains one of the chief causes of the acute abdomen requiring surgery, in spite of its seemingly decreasing incidence as related by Ross[3] and Castleton.[4] This decline has not, however, been noted in England.[5] At present the overall mortality in the United States is 12 per 1,000,000.

Method

A statistical analysis of all appendectomies was compiled in Duluth over a ten-year period 1956 through 1965 from the individual case records of the two general hospitals, St. Luke's and St. Mary's. In this period 4127 appendectomies were performed, divided into three main categories: 1) acute appendectomies, including the normal and simple variety and those with local and general peritonitis; 2) interval appendectomies; and 3) incidental appendectomies of three varieties: pelvic surgery, cholecystectomy, and "other surgery" (Table 1).

Findings in the Appendix

The Inflamed Appendix

The inflamed appendix includes the simple variety, that with local peritonitis such as abscess, etc., and that with general peritonitis: a total of 2046 cases. Pathologically the inflamed appendix is the simple, acute, catarrhal, gangrenous type; periappendicitis; and suppurative varieties with or without an obstructive factor. There were 234 cases of local and general peritonitis, or 12.9% of the acutely inflamed. Hence it would appear that one in eight individuals with acute appendicitis at the time of surgery presents with an advanced form of the disease process, a rather consistent observation conforming nicely with Barnes' study at Massachusetts General Hospital in which the perforated case appears in one out of six appendectomies performed for acute symptoms.

Pathologically there were 290 normal appendices in this series out of 2336 acute cases, representing a 12.4% error in the diagnosis, well within the range of probability when considering the numerous etiologies of the acute abdomen. Further, Howie[6] in Scotland and Elfving[7] in Finland have demonstrated that the mortality in removing a normal appendix is only one in 5,000, compared to a mortality of one in 850 in the same type of patient with acute appendicitis treated medically.

TABLE 1
Appendectomies in Duluth

I. Appendectomies for Acute Symptoms		
a. Normal	290	
b. Simple	1812	
c. Local Peritonitis	161	
d. General Peritonitis	73	
Total Acute Appendectomies		2336
II. Interval Appendectomies	84	
III. Incidental Appendectomies	1707	
a. Pelvic Surgery	757	
b. Cholecystectomy	696	
c. Other	252	
Grand Total		4127

*West Duluth Clinic, Duluth, Minnesota.

The patient with a normal appendix pathologically, who has symptoms of an acute abdomen, is always an enigma, especially if an adolescent. A whole host of pathological processes come to mind. For example, a fecalith may cause appendiceal obstruction and colic with clinical signs of appendicitis; but microscopic examination of the delivered appendix is often found to be normal. Similarly the appendix with oxyuriasis or the long tenuous abdominal appendix with kinking and subsequent obstruction may produce acute symptoms without inflammatory changes. Hence one can justify the removal of an occasional normal appendix in a doubtful case.

Interval Appendectomy

Only 84 cases (5.4%) of the acute appendices were removed as an interval procedure. This procedure is declining annually at approximately 1% per year, suggesting its decreasing necessity with better surgical judgment and care.

Incidental Appendectomy

The incidental appendectomy is always interesting, for the probability of developing acute appendicitis varies with age and sex, males slightly outnumbering females. Ludbrook[8] has demonstrated in New Zealand a probability of 13 in 100 of the general population developing an acute appendix before the age of five years, with a 0.5 in 100 probability at the age of 80, the incidence declining rapidly after the age of twenty. Hence it would seem logical to remove the appendix electively in a younger individual whenever possible. In this series 85.1% of the total 1707 cases of incidental appendectomies were performed with pelvic and gallbladder surgery. Inasmuch as the average age in this group of patients varies between 40 to 50 years, one may postulate that removing the appendix is unnecessary in the vast majority of adults on an incidental and statistical basis.

Wound Infection

Of those 2336 patients operated upon for acute symptoms, 179 (7.2%) developed wound infections. The infection rate was higher in those with peritonitis and in the older patients. In addition, there were eight cases of pelvic abscess and one case of gross peritonitis postoperatively. Barnes[9] has demonstrated that the wound infection rate is variable, with a 1.7% incidence in the "normal", 3.5% in the acute, and 24% in the perforated appendix.

Mortality

The postoperative mortality of the acute appendix in this series was 0.43% (10 cases), comparing favorably with other series. Four patients died of vascular causes, pulmonary emboli phenomena and acute myocardial infarction; three expired from overwhelming sepsis, two from the complications of diabetes mellitus, and one patient from septicemia.

Associated Problems with Acute Appendicitis

Pregnancy

It is often stated that appendicitis is a rare finding in pregnancy. In this series, twelve cases occurred in pregnancy (an incidence of 0.6%), comparable to that found in other series.[10]

Malignancy

Since occult malignancies of the left colon are said to be present in 1 to 3% of patients with acute appendicitis over the age of 60, the acute appendix serves as a "warning" signal in the partially obstructing colonic lesion. In this review three such cases were found. Hence it would be advisable to obtain colon x-rays in the elderly patient within a reasonable time after appendectomy for acute symptoms.

The Surgeon

In determining the surgeon in appendec-

TABLE 2
Pathology in Acute Appendicitis

Type	#	%
Acute Appendicitis	1610	78.7
Fecalith	387	18.9
Oxyuriasis	39	0.2
Adenocarcinoma	3	
Adenoma	2	
Carcinoid	1	
Foreign Body	1	
Villous Adenoma	1	
Actinomycosis	1	
Mucocele	1	
	2046	100%

tomies for acute symptoms, it was observed that the family physician performed 1170 (50.1%), the Duluth Clinic surgeons 361 (15.5%), and the independent surgeon 805 (34.4%).

Etiology

The pathology of acute appendicitis can be observed in Table 2. Fecaliths were observed in only one out of five cases of acute appendicitis.

The adenocarcinoma and carcinoid were limited to the appendix without signs of metastasis. The one case of mucocele was also limited to the appendix, though it may be malignant in nature, as reported by Behling.[11]

Variation in Acute Appendix

Decreasing Incidence

The decreasing incidence of acute appendicitis observed by Ross & Castleton was based on the analysis of local populations and the absolute number of appendectomies performed in the local hospital. It may well be that the declining incidence is secondary to an increasing longevity of the population, making for a relative rather than an absolute decrease. In this small series (Chart 1) there is little variation from year to year. The annual overall average of appendicitis in Duluth is roughly 2 in 1,000, somewhat less than the overall national average.

Age and Sex Distribution

Since 55.0% of the male and 60.3% of the female cases are in the age group 0 to 20 years, one can see that acute appendicitis is primarily an adolescent disease process, male and female duplicating each other statistically, except that the males outnumber the females by approximately 1½ to 1 up to the age of 50 years and 2 to 1 thereafter (Chart 2).

Seasonal Variation in Acute Appendix

Much has been said as to the seasonal variation of the acute appendix. Chart 3 shows that there was a peak of 209 cases in the month of June, the male and female cases 119 and 90, respectively.

Although the least number of appendices were removed in September, the variations are

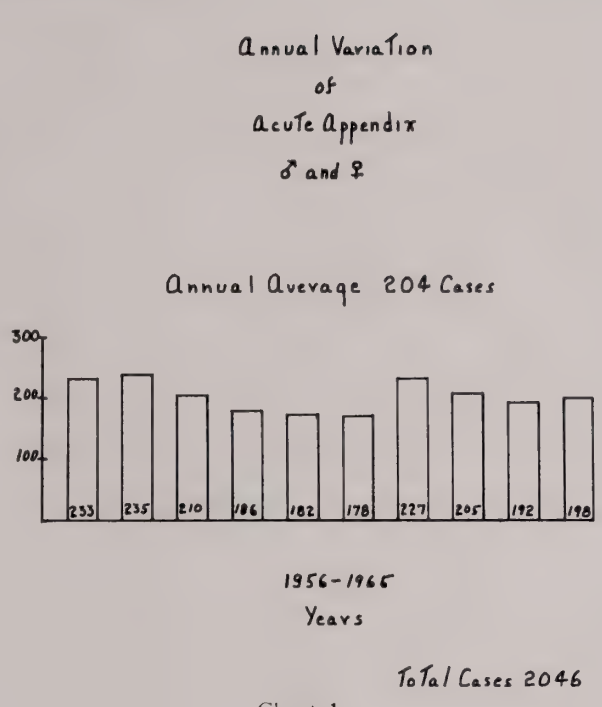


Chart 1

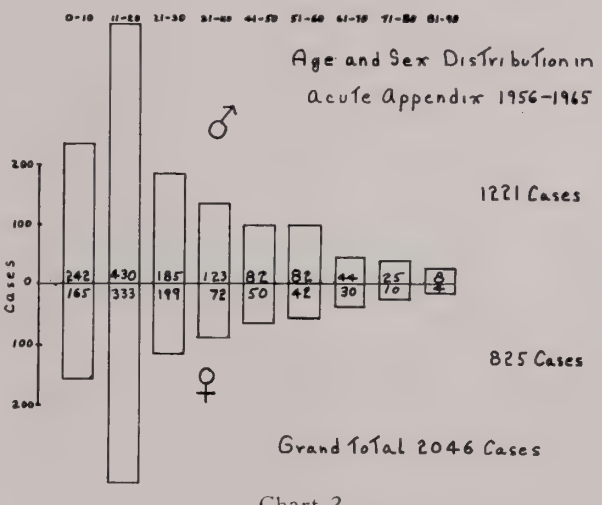


Chart 2

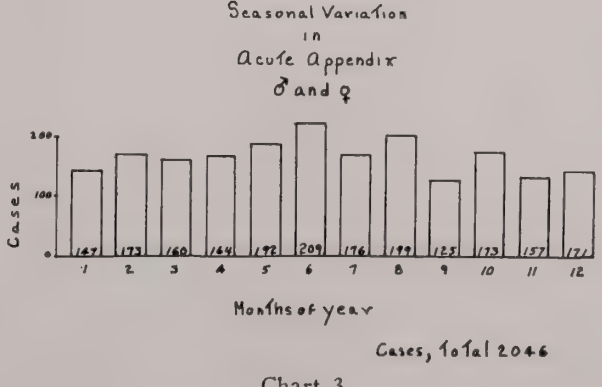


Chart 3

not statistically significant but rather a "barometer" of an increase in acute appendicitis in the late spring and summer months as observed in Chart 4.

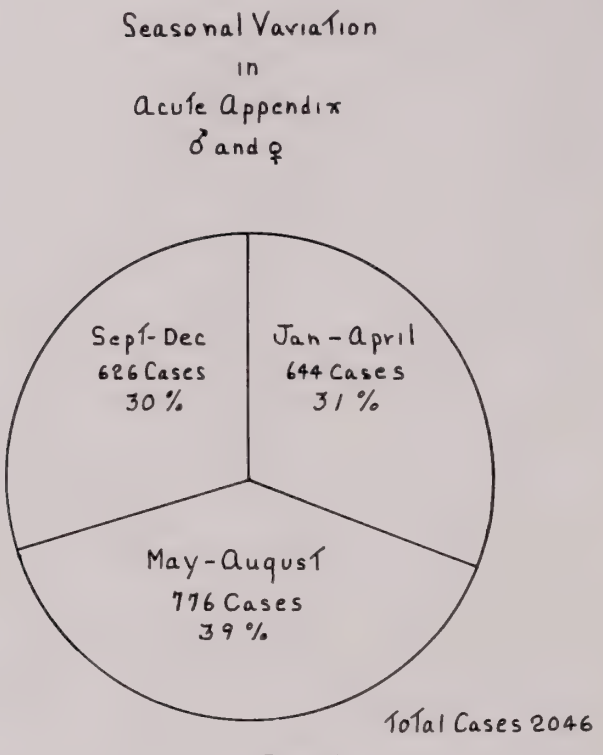


Chart 4

Summary and Conclusions

The incidence of the inflamed appendix in this series was a consistent 2 in 1000 in the general population.

The operative mortality of the acute appendix was .46%, comparing favorably with other series.

Acute appendicitis in pregnancy had an incidence of .6%.

A fecalith was found in the acute appendix in only 18.9% of the cases.

The inflamed appendix is predominantly an adolescent disease, with the majority of cases occurring at 20 years of age, the males outnumbering the females by 1½ to 1.

It would appear that acute cases predominate in the late spring and summer months.

Acknowledgment

I wish to thank the personnel of the Medical Records Departments in St. Luke's and St. Mary's for their help and cooperation in compiling the statistics for this research paper. I also wish to thank Dr. John V. Thomas for his assistance.

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Correction

MINNESOTA MEDICINE carried an article under Law and Medicine on the Minnesota Hospitalization and Commitment Act, and I would like to correct one error which appeared on Page 1418 in connection with the Review Board. In the article it states that the members of the Review Board would receive $30 per day as compensation. Actually, the law allows $50 as compensation and represents the true amount as stated in the law, and we would like your readers to be aware of this.

David J. Vail, M.D.
Medical Director
Department of Public Welfare



NORTHLANDS REGIONAL MEDICAL PROGRAM

REGIONAL PROGRAM FOR HEART DISEASE, CANCER AND STROKE

This article initiates a new regular feature in Minnesota Medicine, designed to help keep you informed about *your* regional medical program.

What is a Regional Medical Program (RMP)?

The law (#89-239) defined the purposes of RMP as follows:

"(a) To encourage and assist in the establishment of regional cooperative arrangements among medical schools, research institutions and hospitals, for research and training (including continuing education) and for related demonstrations of patient care in the fields of heart disease, cancer, stroke and related diseases;

(b) To afford to the medical profession and the medical institutions of the Nation, through such cooperative arrangements, the opportunity of making available to their patients the latest advances in the diagnosis and treatment of these diseases, and

(c) By these means, to improve generally the health, manpower and facilities available to the Nation, and to accomplish these ends without interfering with the patterns, or the methods of financing of patient care or professional practice, or with the administration of hospitals, and in cooperation with practicing physicians, medical center officials, hospital administrators, and representatives from appropriate voluntary health agencies."

Who Organized the Minnesota Program?

The key to RMP is cooperative arrangements. In Minnesota, nine organizations cooperatively developed Northlands Regional Medical Program—Minnesota State Medical Association, Minnesota Hospital Association, University of Minnesota College of Medical Sciences, Mayo Foundation, Minnesota State Board of Health, Minnesota Heart Association, Minnesota Cancer Society, American Rehabilitation Foundation, and Minnesota State Medical Association Foundation.

What is the Objective of the Program?

The focus is on the patient. Each region is asked to define its geographic boundaries, identify its needs, outline its objectives and develop programs whereby each patient can receive the benefits of the latest scientific knowledge.

What are the Problems?

Each of you has problems in the practice of medicine such as: How can I find practical information on the latest diagnostic and treatment methods for x, y and z diseases? Where can I get the reliable laboratory and other diagnostic tests which I need? How can I get necessary consultations? How do I get hospitals and necessary paramedical disciplines to take over an increasing share of medically related responsibilities? How do I get some help for the stupendous work-load?

There are plenty of additional problems—it is certain that each of you could contribute a dozen more.

Northlands Regional Medical Program is a federally supported venture to help Minnesotans solve their problems of delivery of medical care services, to the end that each patient may have the benefits of the latest in modern medical knowledge. The challenge is great—we hope the willingness to cooperate can be stimulated in the Medical Centers and among the practicing profession.

Addendum

The philosophy ably expressed by Dr. Ciriacy* in "President's Letter" last month is closely analogous to the philosophy of Northlands Regional Medical Program. Can we all work together to distill the "Ferment in Medicine" in Minnesota? As expressed by John W. Gardner on educational television, we need "grass roots leadership" to counteract the adverse effects of "sophisticated dropouts" and "sidewalk superintendents."

Winston R. Miller, M.D., F.A.C.P.
Program Director

*See Minnesota Med 51:173, 1968.

The Unsureness of Science

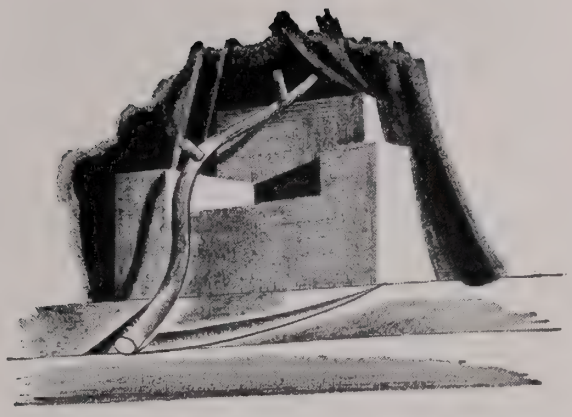
Let no man be so foolish as to think that he has exhausted any subject for his generation. Virchow was not happy when he saw the young man pour into the old bottles of cellular pathology the new wine of bacteriology. Lister could never understand how aseptic surgery arose out of his work. Ehrlich would not recognize his epoch-making views on immunity when this generation has finished with them. I believe it was Hegel who said that progress is a series of negations—a denial today of what was accepted yesterday, the contradiction by each generation of some part, at least, of the philosophy of the last; but all is not lost, the germ plasm remains, a nucleus of truth to be fertilized by men, often ignorant even of the body from which it has come. Knowledge grows, but in such a way that its possessors are never in sure possession. "It is because science is sure of nothing that it is always advancing." (Duclaux)*

*William Osler in Richard Magraw; Ferment in Medicine, 1966.

The "1968 Directory of Referral and Rehabilitation Resources," is available to physicians in limited supply without charge. This revision was compiled by W. W. Keenan. It is available by request from:

Mr. G. Dean Miller, Consultant
Pupil Personnel Services Section
Department of Education
Fourth Floor, Centennial Building
St. Paul, Minnesota 55101

I wonder why ye can always read a doctor's bill an ye niver can read his purscription.—Finley Peter Dunne



In Memoriam

That last day does not bring extinction to us, but change of place.—Cicero

We begin to die as soon as we are born, and the end is linked to the beginning.—Manilius

MARIO McC. FISCHER, M.D.

Dr. Mario McC. Fischer, 68, executive health officer of St. Louis County until his retirement last July, died January 15. A native of Minneapolis, Dr. Fischer had practiced in Duluth since 1926.

He was a member of the Minnesota Public Health Conference, the American Public Health Association, the American Medical Association, and the St. Louis County Medical Society. He was an associate member of the Minnesota State Medical Association. Dr. Fischer served as president of the National Tuberculosis Association, as director of the Tuberculosis and Health Association of St. Louis County, the Duluth Mental Hygiene Association, the Duluth Chapter of the Minnesota Cancer Society and the South St. Louis County Chapter of the National Foundation.

Dr. Fischer was the recipient of the Minnesota Public Health Association's Chesley Award, the group's highest award.

He is survived by his wife and two sons.

WILLIAM A. KLEIN, M.D.

Dr. William A. Klein, 59, Duluth orthopedic surgeon, died January 16. He had practiced medicine in Duluth since 1946. Born in St. Peter, he received his medical degree at the University of Minnesota.

Dr. Klein was a member of the St. Louis County Medical Society, the American Board of Orthopedic Surgeons and the American Medical Association and an associate member of the Minnesota State Medical Association.

He is survived by his wife, two daughters and a son.

PETER C. ENGELHART, M.D.

Dr. Peter C. Engelhart, 71 Minneapolis physician, died December 30. Born in Mazeppa, Minnesota, Dr. Engelhart received his medical education at the University of Minnesota.

He was a member of the American Medical Association and the Hennepin County Medical Society and an associate member of the Minnesota State Medical Association.

He is survived by his wife and two children.

RAUEN A. CURTIS, M.D.

Dr. Rauen Curtis, 60, Le Center physician, died November 6. Born in Osseo, Dr. Curtis obtained his medical degree from the University of Minnesota Medical School.

He was a member of the American Medical Association, Nicollet-LeSueur County Medical Society and the Minnesota State Medical Association.

He is survived by his wife.

MORSE J. SHAPIRO, M.D.

Dr. Morse J. Shapiro, former clinical director of pediatrics and medicine at the University of Minnesota Medical School who helped establish the Variety Club Heart Hospital in Minneapolis, died February 11, in West Los Angeles, California. He was 74 years of age. In 1951 he moved to California when he became chief of pediatric cardiology at Cedars of Lebanon Hospital.

He established and directed a clinic in Minneapolis for children who were victims of rheumatic fever, which gave impetus to the building of the Variety Club Heart Hospital. In 1955 he received the University's first special commendation for distinguished achievement as a pioneer in scientific knowledge in the heart field.

He is survived by his wife, a daughter and a son, Dr. Marvin Shapiro of Sherman Oaks, California.

Help America get ahead

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Social Security

Retirement Benefits for Physicians under Social Security

SELF-EMPLOYED DOCTORS have been paying the Social Security tax on their net earnings for three years and therefore in 1968 physicians who have attained the age of 70 are now eligible to receive Social Security payments if their net earnings do not exceed $1,680 per year.

To be retired for Social Security purposes means either that the doctor's yearly net income is limited to $1,680 or he does not perform a substantial amount of service in one or more months in the year. If this 70-year-old physician takes a vacation or becomes ill for one or more calendar months and does not work at his practice, he is considered retired for that month and can receive Social Security benefits of $157.80 (see Table).

After a physician's seventy-second birthday there are no restrictions on the earnings, and he is eligible to obtain Social Security benefits regardless of the earnings from his practice. If he continues to earn $6,600 or more, his Social Security benefits can increase from year to year as indicated in the Table.

The doctor (and wife) who has been on a salary for many years, now age 65, can retire in 1968 with Social Security benefits of $238.20 per month. If he does not retire, however, his Social Security benefits will continue to increase from year to year. The maximum increase in Social Security benefits for doctor and wife may reach $323.00 per month (see Table).

It must be remembered, however, that circumstances are variable in almost every instance, and for an accurate evaluation of your own Social Security status it is advisable to call the Social Security Administration District Office.

TABLE
SELF-EMPLOYED SOCIAL SECURITY BENEFITS
FOR PHYSICIANS

Age in 1968	Dr. & Wife February 1968	Dr. & Wife January 1969	Dr. & Wife January 1970	Dr. & Wife January 1971	Dr. & Wife January 1972	Dr. & Wife January 1973	Dr. & Wife January 1974	Dr. & Wife January 1975	Dr. & Wife January 1976
65	NONE	NONE	$152.40	$163.40	$174.30	$183.30	$190.70	age 72 $197.90	$205.20
66	NONE	NONE	157.80	170.60	181.50	190.70	age 72 197.90	205.20	212.30
67	NONE	$150.80	165.20	177.90	188.70	age 72 197.90	205.20	212.30	219.60
68	NONE	157.80	174.30	187.10	age 72 197.90	206.90	214.20	221.40	228.80
69	NONE	167.10	183.30	age 72 195.30	206.90	216.00	225.00	230.40	237.30
70	$157.80	179.70	age 72 196.10	208.70	219.60	228.80	235.70	242.40	247.50
71	172.50	age 72 194.10	210.60	223.40	234.00	240.80	247.50	254.30	257.70
		(There are no restrictions on earnings after 72nd birthday)							
72	190.70	214.20	230.40	240.80	251.00	257.70	262.80	267.90	271.20
73	190.70	240.80	254.30	262.80	271.20	276.30	281.40	284.90	288.00
74	190.70	240.80	288.00	295.50	300.00	303.00	306.00	307.50	309.00
75	190.70	240.80	288.00	310.50	312.00	*315.00	*316.00	*316.00	*317.00
76	190.70	240.80	288.00	310.50	*317.00	*318.00	*319.00	*319.00	*320.00
77	190.70	240.80	288.00	310.50	*317.00	*323.00	*323.00	*323.00	*323.00

*Wife Maximum $105.00

Figures to the left of the heavy line step graph indicate the benefits paid if the physician quits work though he may have a net earning of $1,680 or less. Figures to the right of the step graph indicate the increasing Social Security benefits that can be received if the physician continues to work and earn a net of more than $6,600.


in moderate hypertension and
poorly controlled mild hypertension
(when diuretics or sedatives are inadequate, for example)

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like relief from hypertensive symptoms
(headache, fatigue, nervousness, palpitation or insomnia, for example)

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(a schedule not unlike timed-release medication, for example)

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(at 10¢ a tablet, for example)

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...give them a little
(one tablet daily)

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chlorthalidone 50 mg., reserpine 0.25 mg.

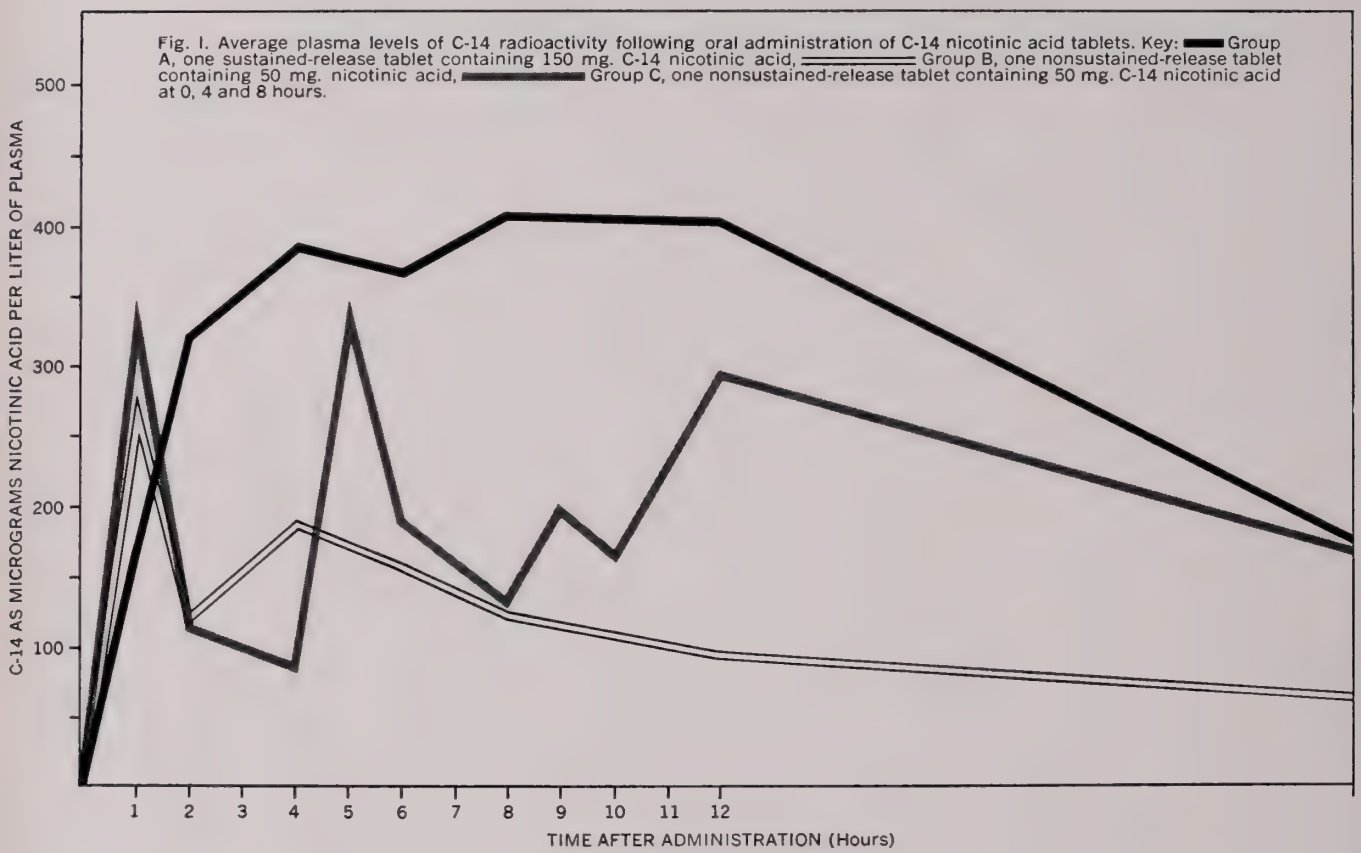
Indications: Hypertension. **Contraindications:** History of mental depression, hypersensitivity, and most cases of severe renal or hepatic diseases. **Warning:** With the administration of enteric-coated potassium supplements, which should be used only when adequate dietary supplementation is not practical, the possibility of small-bowel lesions (obstruction, hemorrhage, and perforation) should be kept in mind. Surgery for these lesions has frequently been required and deaths have occurred. Discontinue coated potassium-containing formulations immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur. Discontinue one week before electroshock therapy, and if depression or peptic ulcer occurs. *Use in pregnancy:* Regroton should be used in pregnant patients or in women of childbearing potential only when, in the judgment of a physician, its use is deemed essential to the welfare of the patients; adverse reactions (thrombocytopenia, hyperbilirubinemia, altered carbohydrate metabolism, etc.) are potential problems in the newborn.
Precautions: Antihypertensive therapy with Regroton should always be initiated cautiously in postsympathectomy patients and in patients receiving ganglionic blocking agents, other potent antihypertensive drugs, or curare. Reduce dosage of concomitant antihypertensive agents by at least one-half. To avoid hypotension during surgery, discontinue Regroton therapy two weeks prior to elective surgical procedures. In emergency surgery, use, if needed, anticholinergic or adrenergic drugs or other supportive measures as indicated. Because of the possibility of progression of renal damage, periodic kidney function tests are indicated. Discontinue if the BUN rises or liver dysfunction is aggravated. Hepatic coma may be precipitated. Electrolyte imbalance, sodium and/or potassium depletion may occur. If potassium depletion should occur during therapy, Regroton should be discontinued and potassium supplements given, provided the patient does not have marked oliguria. Take particular care in cirrhosis or severe ischemic heart disease and in patients receiving corticosteroids, ACTH, or digitalis. Salt restriction is not recommended. Use cautiously in patients with ulcerative colitis or gallstones (biliary colic may be precipitated). Bronchial asthma may occur in susceptible patients. **Adverse Reactions:** The drug is generally well tolerated. The most frequent side effects are nausea, gastric irritation, vomiting, diarrhea, constipation, muscle cramps, headache, dizziness and acute gout. Other potential side effects include angina pectoris, anxiety, depression, bradycardia and ectopic cardiac rhythms (especially when used with digitalis), drowsiness, dull sensorium, hyperglycemia and glycosuria, hyperuricemia, lassitude, restlessness, transient myopia, impotence or dysuria, orthostatic hypotension which may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics, leukopenia, aplastic anemia, skin rashes, thrombocytopenia, agranulocytosis, nasal stuffiness, increased gastric secretions, nightmare, purpura, urticaria, ecchymosis, weakness, uveitis, optic atrophy and glaucoma, and pruritus. Eruptions and/or flushing of the skin, a reversible paralysis agitans-like syndrome, blurred vision, conjunctival injection, increased susceptibility to colds, dyspnea, weight gain, decreased libido, dryness of the mouth, deafness, anorexia, and pancreatitis when epigastric pain or unexplained G.I. symptoms develop after prolonged administration. Jaundice, xanthopsia, paresthesia, photosensitization and necrotizing angiitis are possible. **Average Dosage:** One tablet daily with breakfast. **Availability:** Pink, single-scored tablets in bottles of 100 and 1000. (B) 46-600-B
For details, see complete Prescribing Information.

Geigy Pharmaceuticals, Division of
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Geigy

Sustained circulatory, respiratory and cerebral stimulation for the

Fig. I. Average plasma levels of C-14 radioactivity following oral administration of C-14 nicotinic acid tablets. Key: ▬ Group A, one sustained-release tablet containing 150 mg. C-14 nicotinic acid, ═══ Group B, one nonsustained-release tablet containing 50 mg. nicotinic acid, ▬▬ Group C, one nonsustained-release tablet containing 50 mg. C-14 nicotinic acid at 0, 4 and 8 hours.





(fewer absent doses by absent-minded patients)

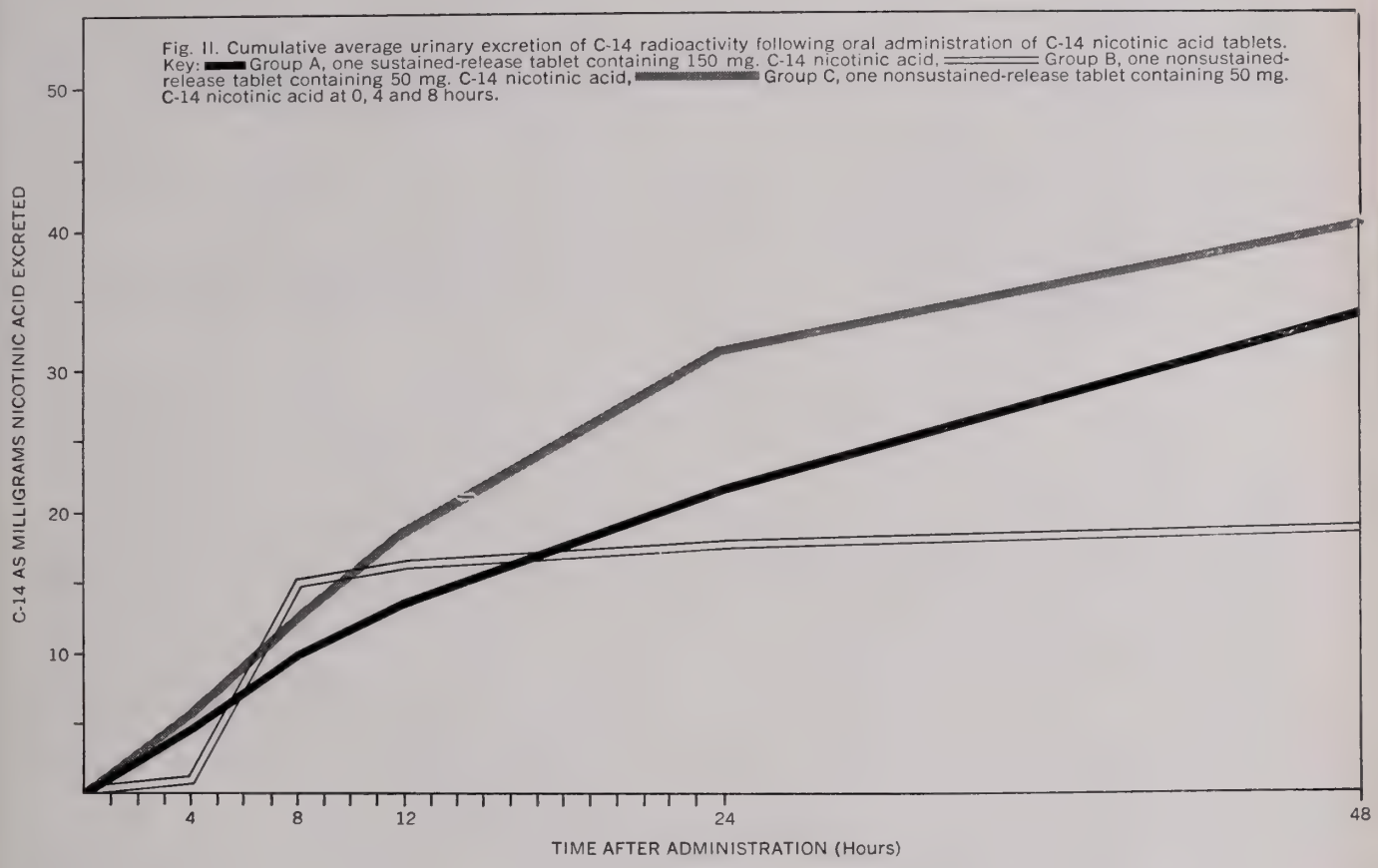
Human volunteer subjects were administered Geroniazol TT tablets with the nicotinic acid component made radioactive with C-14. Plasma and urine samples were analyzed. (See Figures I and II) The radioactive tracer study substantiated the previous clinical evidence that the release of nicotinic acid from the Geroniazol TT tablet produced a gradual rise in plasma levels to a plateau for a total of 12 hours and more.

Such proven sustained activity makes the management of geriatric patients much easier by minimizing the possibility of neglected doses through absent-mindedness or senile confusion. Therapy *can* be continuous on a daily dose of only one Geroniazol TT tablet every 12 hours.

The gradual release of nicotinic acid in Geroniazol TT will provide the well-known peripheral vasodilatation needed in patients with deficient circulation and with a minimum amount (if any) of "flushing." Also, cerebrovascular circulation is complemented by pentylenetetrazol, long-established as a cerebral and respiratory stimulant.

Geroniazol TT improves the typical, unfortunate, signs of senile confusion. Patients become more alert,

aged and debilitated



less confused and moody. Personal care, memory, emotional stability, social attention improve. Fatigue, apathy and irritability are reduced.

A prescription for 100 tablets of Geroniazol TT will permit your patients to enjoy the benefits of time-prolonged nicotinic acid/pentylenetetrazol therapy, at an economical price. Dosage is only one tablet every 12 hours.

Contraindications: There are no known contraindications.

Precautions: Exercise caution when treating patients with a low convulsive threshold.

Side Effects: Side effects are rarely encountered, however due to the vasodilatation effect of nicotinic acid, transitory mild nausea, flushing, tingling and pruritus are possible.

Dosage: One tablet every 12 hours.

Supplied: Prescribe bottles of 100 tablets, to take advantage of recent price reduction.

References: 1. Report by Nuclear Science & Engineering Corp., Pittsburgh, Pa., in files of Philips Roxane Laboratories. 2. Connolly, R.: W. Virginia Med. J. *56*:263 (Aug.) 1960. 3. Curran, T. R., and Phelps, D. K.: Am. Pract. & Digest Treat. *11*:617 (July) 1960.

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Tempotrol® Time Controlled Tablet



Meetings and Announcements

An idea isn't responsible for the people who believe in it.—Don Marquis

MARCH

Southwestern Minnesota Medical Society, March 4, Ehlers Supper Club, 7:00 P.M.

Scott-Carver County Medical Society, March 5, Wagner Supper Club, Jordan, 7:30 P.M.

Zumbro Valley Medical Society, March 6, Regular Meeting, Plummer Hall, 7:00 P.M.

Minnesota Academy of Ophthalmology and Otolaryngology, March 8, Minnesota Club, St. Paul, 6:30 P.M.

Diabetic Detection and Education Center, March 9, All day symposium on diabetes at the Diabetes Center—916 E. 15th Street, Minneapolis.

Hennepin County Medical Society, March 11, Joint meeting with Minneapolis Surgical Soc., Mpls. Pediatric Society, Henn. Cty. Academy of Gen'l Practice, and Henn. County Psychiatric Society.

West Central Minnesota Medical Society, March 12, Regular Meeting with Speaker, Morris, 8:00 P.M.

Minnesota Academy of Medicine, March 13, Town and Country Club, St. Paul, 7:00 P.M.

Camp Release District Medical Society, March 14, Monthly Meeting, Hunt Hotel, Montevideo, 7:30 P.M.

St. Louis County Medical Society, March 14, Executive Committee, St. Mary's Hospital, 6:00 P.M.—Regular Meeting, St. Mary's Hospital, 8:00 P.M.

Twin City Urological Society, March 15, Town and Country Club, St. Paul, 6:30 P.M.

Steele County Medical Society, March 19, Inntown Motel, Owatonna, 6:30 P.M.

Blue Earth Valley Medical Society, March 20, Regular Meeting, Interlaken Golf Club, Fairmont, 7:00 P.M.

Kandiyohi-Swift-Meeker County Medical Society, March 21, Westwood Inn, Spicer, 7:00 P.M.

McLeod County Medical Society, March 21,

Blue Earth County Medical Society, March 25, Century Club, 8:00 P.M.

Range County Medical Society, March 26, General and Executive Meetings, 7:00 P.M.
Dinner Meeting, Hibbing

Northwestern Pediatric Society, March 29, Neurology Seminar, University Club, St. Paul, 6:00 P.M.

Minnesota Society of Anesthesiologists, March 30, Dinner Meeting, 6:00 P.M. (place to be announced)

American College of Physicians will sponsor a three-day postgraduate course "The Clinical Selection of Patients for Cardiac Surgery" March 14-16, Rochester, Minnesota, at the Mayo Graduate School of Medicine, University of Minnesota and the Mayo Clinic. For registration contact: Edward C. Rosenow, Jr., M.D., American College of Physicians, 4200 Pine Street, Philadelphia, 19104.

Spring refresher course for American Board Candidates in obstetrics and gynecology will be held at Marquette School of Medicine, Milwaukee, March 18-22. Contact: Office of Continuing Education, Marquette School of Medicine, 561 North 15th Street, Milwaukee 53233.

The Minnesota Thoracic Society and the Minnesota Respiratory Health Association announce a second award contest for medical students, interns and resident physicians in Minnesota.

(A) An award of $200.00 is offered for the best paper submitted by a senior medical student or intern on some aspect of respiratory disease, preferably based upon laboratory or clinical investigation.

(B) An award of $300.00 is offered for the best paper submitted by a resident physician based upon clinical or laboratory investigation in the area of respiratory disease.

Further information may be obtained from the Secretary. Entries should be submitted by September 1, 1968 to: David E. Dines, M.D., Secretary, Minnesota Thoracic Society, Mayo Clinic, Rochester, Minnesota.

L. E. Phillips Psychobiological Research Divisions of North Memorial and Mount Sinai Hospitals with The Minnesota Heart Association Symposium on Heart and Emotions. North Memorial Hospital auditorium, April 7, 1968. Afternoon and evening sessions (1:15 p.m. to 8:45 p.m.), with dinner being served at 5:30 in the hospital dining room. Attendance has been approved by the Academy of General Practice for 6 hours of Post-Graduate Study. Since the number of registrants will be limited, they will be accepted by acknowledgment in the order received. Contact Ralph Rossen, M.D., 588-0616, extension 301, or 339-1692, extension 596.

Minnesota Medicine at a Glance

Reye's Syndrome—Mack Page 335

Rare diseases continue to be rare as long as physicians are content to misfile problems under old disease categories. They are not so rare when the unsatisfied observer works out the problem. This article contains the 128th reported case of a child with encephalopathy and fatty degeneration of the viscera. That this usually fatal disease may be much more common in a non-fatal form is suggested by the tendency to recovery observed in the child before unexpected and unanticipatable complications of drug idiosyncrasy caused his death.

Coronary Arteriography—Lee and Amplatz Page 343

Selective coronary arteriography is the radiographic method of choice in evaluating coronary artery anatomy and pathology. Attempts of non-selective coronary arteriography frequently result in poor opacification of one or more major coronary branches. Inadequate visualization and poor opacification may lead to erroneous diagnoses. In addition, selective coronary arteriography can provide information such as inter-coronary anastomoses or coronary arteriovenous fistulae that are difficult to demonstrate by non-selective aortography. The risk of selective and non-selective coronary arteriography in our experience is identical.

Upper Lip Nodules—Erich and Jamra Page 347

A review of nodules in the upper lip of patients treated at the Mayo Clinic from 1944-1963 is presented. Eighty-six percent were neoplasms and the importance of adequate treatment is stressed.

My Grandfather Made Me Wish to Become a Doctor

Probably I should never have known that the Boston Lying-in Hospital existed, nor indeed should I ever have studied medicine, had not my maternal grandfather, when I was a small boy, unknowingly and unintentionally made me wish to become a doctor.

As Assistant Surgeon in the Thirty-Fifth New York Infantry my grandfather had joined the Union Army soon after the outbreak of the Civil War. His story of the bloody aftermath of conflict, of his work among the maimed and dying, was strong meat for a boy of ten; but its sole effect on me was to sharpen my appetite for more.

The relationship between my grandfather and myself was of a particular and private nature. When he talked to me it was always as if I were of his own age; there was no painful simplicity of words, no tedious explanations. If he had known that I wished to become a doctor, I am sure he would have been displeased, for his life had been a hard one, and it would have pained him to picture a similar experience for me; so I kept my counsel.*

Editor's Note: *Frederick Irving served in World War I and later became consulting obstetrician to the Boston Lying-in Hospital.*

---

*Frederick C. Irving (1883-) in "Why We Became Doctors" edited by Noah Fabricant, M.D., 1954.

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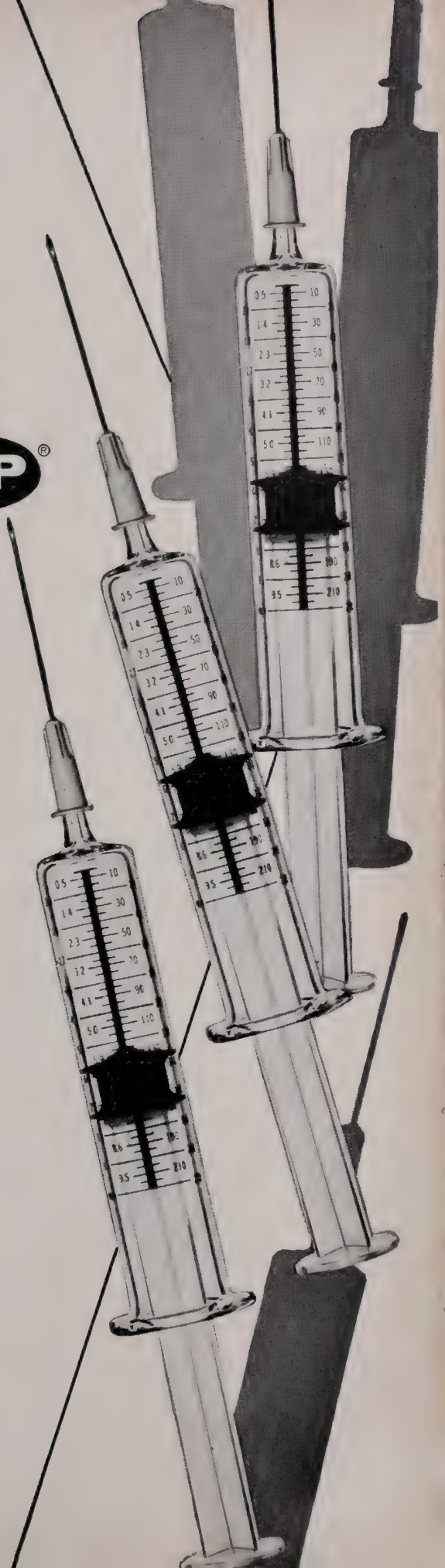


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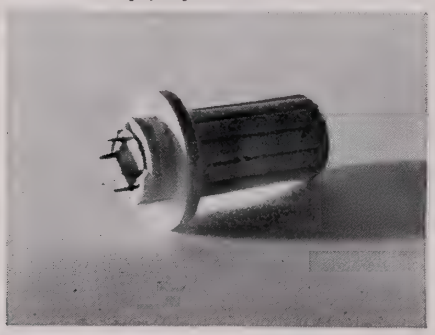
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President's Letter

Quality Care-Concerned Care

WHEN ELECTED by my colleagues in the Minnesota Society of Internal Medicine I felt very much honored. Now, being expected to provide some written thoughts worthy of the time and the attention of the readers of this Journal, finds me anxious to do just that. My anxiety mounts as I consider the best way to discuss the subject I feel needs some emphasis. The emphasis is general and not aimed at any specific group because the subject is not group-specific.

With increasing government-sponsored medical care and increasing amounts of "third-party" participation in the financial aspect of medicine, doctors of medicine of whatever persuasion, specialty, or organization have become increasingly apprehensive that these "outside" forces might in some way result in an inferior quality of medical care. At least this apprehension has been the "sacred cow" on which much of our organized objection to these programs has been based, and perhaps rightly so. At any rate, there has been considerable scurrying about on the part of medical organizations to "establish our perimeters"—set up standards or criteria which would clarify the various types of medical or surgical care, and thereby also establish commensurate fee schedules. We now have "relative-value" schedules which help delineate certain types of medical care and their attendant financial remuneration, but really no guarantee of a higher quality of medical care.

We also now have Medicare, full-fledged and apparently burgeoning, with perhaps new election-year expansions ahead. We have had some problems in the mechanics of operation of the programs, but from my vantage point I do not see any increased evidence of deteriorated medical care. We still have the human errors of judgment, miscalculation, and carelessness; even some of the former evidence, unfortunately, of frankly false medical care, but no great upsurge. Perhaps we can credit some of this upholding of quality to the very measures organized medicine has been able to include in the legislative programs. But I prefer to give credit in another direction.

From my day-to-day experience I judge my colleagues to be continuing to give their best to the care of their patients, and I also observe this in the majority of the young men in training with whom I have come in contact. As I try to explain this continuing attempt to render quality medical care, I cannot believe it results mainly from concern for establishing a system for furthering personal gains. Instead of concern for self it arises, I believe, out of concern for the patient. We have, over the years, tended to extol the "doctor-patient relationship" and protect it as a "holy grail." Concern for the patient as a person is to my mind the best means of minimizing those human errors of poor judgment, miscalculation, and carelessness; that concern should totally eliminate frankly false medical care. Surveys which have shown the marked disparity between a layman's high appreciation and approval of a known doctor and the far lower ratings of doctors in general reflect this factor. When one believes his doctor is concerned, he feels he is in better hands than with an indifferent doctor.

We need not reemphasize the importance of top-quality medical facilities, training, and continuing education. But perhaps we can benefit by refocusing on a major determinant of the best medical care—a real concern for the patient; and avoid the blurring of our goal by so many other anxiety-producing factors in our society.

Mark C. L. Hanson, M.D., President
Minnesota Society of Internal Medicine

STATE MEDICAL ASSOCIATION

minnesota medicine

Volume 51

Number 4

PRESIDENT'S LETTER 473

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Minneapolis, Minnesota

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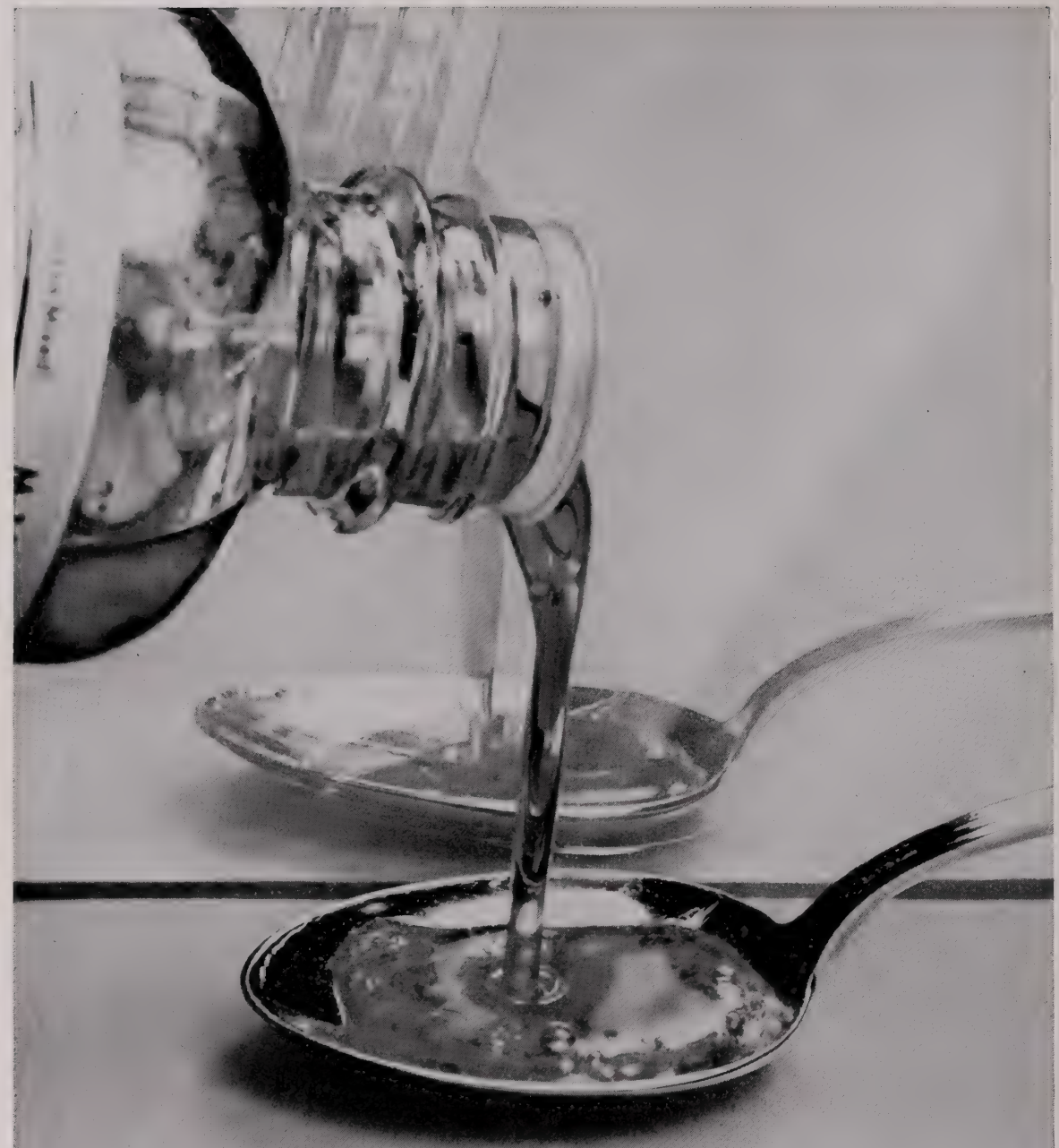
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Severe Atherosclerotic Cardiovascular Disease

In a 14-Year-Old Homozygous Familial Hypercholesterolemic*

HENRY BUCHWALD, M.D., Ph.D.**
GERALD B. LEE, M.D.
KURT AMPLATZ, M.D.
RICHARD B. MOORE, M.D.
IVAN D. FRANTZ, JR., M.D.
RICHARD L. VARCO, M.D., Ph.D.
Minneapolis, Minnesota

FAMILIAL HYPERCHOLESTEROLEMIA is the most common cause of atherosclerosis in the pediatric age group. Recognition of this disease started with the descriptions of xanthomatous lesions by Rayer[1] in 1826 and by Addison and Gull[2] in 1851; the familial nature of the disturbance was pointed out in the latter part of the nineteenth century.[3-6] Chaufford and LaRoche[7] in 1910 first associated the state of xanthomatosis with hypercholesterolemia in the presence of liver disease; ten years later Burns[8] reported a patient with xanthomata and hypercholesterolemia who was free of liver disease. Arterial involvement as part of the syndrome was known as early as 1872,[9] but a definite correlation in young patients of premature atherosclerosis with familial hypercholesterolemia was well-documented only in the late 1940s and early 1950s in a series of papers by Adlersberg and Boas.[10-12] Genetically, familial hypercholesterolemia is thought to be due to a dominant gene with incomplete penetrance.[13-15]

The occurrence of a true homozygous† (type II) hypercholesterolemic individual is rare indeed, depending as it does on the small chance of conjugation between people carrying the gene for the Fredrickson type II hyperlipidemia,[16] as well as on Mendelian probability. Such unfortunate individuals have, in essence, a "double dose" of the disease, and their rate of development of atherosclerotic cardiovascular manifestations can be expected to be greatly accelerated. The homozygous hypercholesterolemic patient usually presents a unique pattern of findings: the individual is in his teens or younger, arcus senilis is present, subcutaneous and tendon xanthomata are evident, atherosclerotic fundic changes can be seen, and the patient commonly complains of severe exer-

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**Established Investigator, American Heart Association. Dr. Buchwald was given the Gross Award by the Philadelphia Academy of Surgery at their annual meeting for his overall approach to this problem.

†See Test Your Word Score Page 511.

tional angina pectoris. An early death from myocardial infarction is to be expected. A characteristic lesion of these patients is acquired aortic valvar stenosis and/or, occasionally, aortic valvar insufficiency,[17,18] both due to heavy accumulations of proliferative atherosclerotic plaques in the valve and adjacent aortic wall. Similar plaques can also involve the orifices of the coronary arteries.

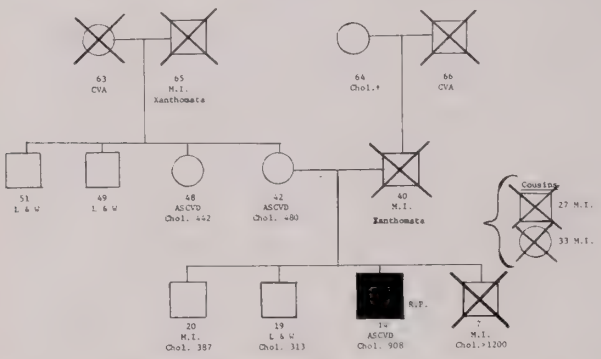


Fig. 1—Diagram of family tree.



Fig. 2—Subcutaneous xanthomatous lesions over the elbows of patient R.P.



Fig. 3—Subcutaneous xanthomatous lesions over the knees of patient R.P.

This case history describes a 14-year-old homozygous hypercholesterolemic boy with far-advanced atherosclerotic coronary heart disease, and reviews our diagnostic and therapeutic approaches to this problem.

Report of a Case

History

R. P. was the product of a normal birth and gestation with both parents having familial xanthomatosis. Massive subcutaneous and tendon xanthomata appeared a few years after birth. At one time, some of these lesions were surgically removed. His cholesterol level has always been around 1000 mg%. This value was maintained despite efforts to keep the boy on a stringent, low-cholesterol, low saturated-fat diet since birth. In addition, he was treated, from time to time, with nicotinic acid and, more recently, with cholestyramine, both without significant effect on his serum cholesterol level. At about the age of nine he developed definite exertional angina pectoris, the severity of which progressed over the years. When we first saw him one year ago he was no longer able to participate in the normal activities for boys of his age. He was essentially limited to a sedentary existence.

Family History

The family history has been traced back to both sets of grandparents and is graphically illustrated in Figure 1. It can be seen that R.P.'s maternal grandparents both died of coronary or cerebral vascular manifestation of atherosclerosis. His paternal grandfather died of a cerebral vascular accident; his paternal grandmother is living, age 63, and has a high serum cholesterol level and xanthomatosis. His father died at the age of 40 of an acute myocardial infarction. The boy's mother is alive, has sustained a cerebral vascular accident, and has coronary angiographic evidence of marked occlusive disease. Her serum cholesterol (prior to an ileal bypass operation) averaged 480 mg% despite dietary management. Her blood cholesterol level was also refractory to nicotinic acid and cholestyramine. R.P.'s siblings consist of two living brothers and one dead brother. The oldest living brother, age 20, had a myocardial infarction 1½ years ago; his serum cholesterol level was 387 mg% prior to a partial ileal bypass operation. He had no angina pectoris before or after his myocardial infarction and has no angiographic evidence of aortic root involvement. The next oldest brother is now 19 and has a serum cholesterol level of 313 mg%; he is completely free, symptomatically and angiographically, of any manifestations of atherosclerotic cardiovascular disease and has no peripheral xanthomatoses. The youngest brother died at the age of

seven, presumably of an acute myocardial infarction while experiencing severe crushing chest pain. His cholesterol level had been over 1200 mg%.

Physical Examination

On admission to the University of Minnesota Hospital, R.P.'s pulse rate was regular at 80 and his blood pressure was recorded at 130/70. Advanced arcus senilis was evident. There were multiple subcutaneous xanthomatous lesions, primarily over the elbows (Figure 2) and over the knees (Figure 3). Large, partially resected, bilateral Achilles tendon xanthomata were present. Harsh and loud bruits could be heard over most of his major vessels, including the iliac, femoral, and carotid arteries bilaterally. A grade V/VI systolic murmur was heard over the entire precordium with maximum intensity to the right of the sternum in the second intercostal space. There was a left ventricular heave, a suprasternal notch thrill, and P_2 was louder than A_2 with no apparent split.

Laboratory Data

Routine hematology, coagulation studies, and blood electrolytes were all normal, with the exception of a somewhat elevated uric acid level of 6.2 mg%. The fasting blood sugar level was normal at 79 mg%, as was the two-hour post-prandial reading of 84 mg%. The serum cholesterol levels over 11 consecutive days ranged between 832 mg% and 1012 mg%, with an average value of 908 mg%. Lipid evaluation carried out at the Bio-Science Laboratories* gave a cholesterol value of 1050 mg%, serum phospholipids of 684 mg%, serum triglycerides of 147 mg%, and total lipids of 2,351 mg% (see Figure 5 for comparison of preoperative values and post-ileal bypass determinations). On serum lipoprotein electrophoresis an extremely prominent beta band characteristic of type II familial hyperlipidemia was seen.

Posteroanterior and lateral x-ray projections of the chest showed clear lung fields and no apparent cardiac enlargement. The oral cholecystogram revealed normal emptying and no evidence of stones. The aortogram (Figure 4) showed a markedly irregular and narrowed ascending aorta and arch due to atherosclerotic plaque deposits. A systolic pressure difference of approximately 50 mm.Hg. across the aortic valve was present at rest and there was radiographic evidence of aortic regurgitation in association with slight enlargement of the left ventricular cavity. Mild mitral regurgitation was also seen. The coronary arteries were diffusely diseased with the left anterior descending coronary artery primarily involved. (Selective coronary angiography could not be carried out because of the severity of the disease at the coronary ostia.) Left ventricular hypertrophy was evident on the electrocardiogram; this was confirmed by the vectorcardiogram. The carefully monitored double two-step test electrocardiogram was strongly positive with significant ST depressions immediately

*Bio-Science Laboratories, 7600 Tyrone Avenue, Van Nuys, California.



Fig. 4—Aortogram revealing severe atherosclerotic deposits in the root of the aorta and in the aortic valve leaflets, resulting in aortic stenosis and aortic insufficiency.

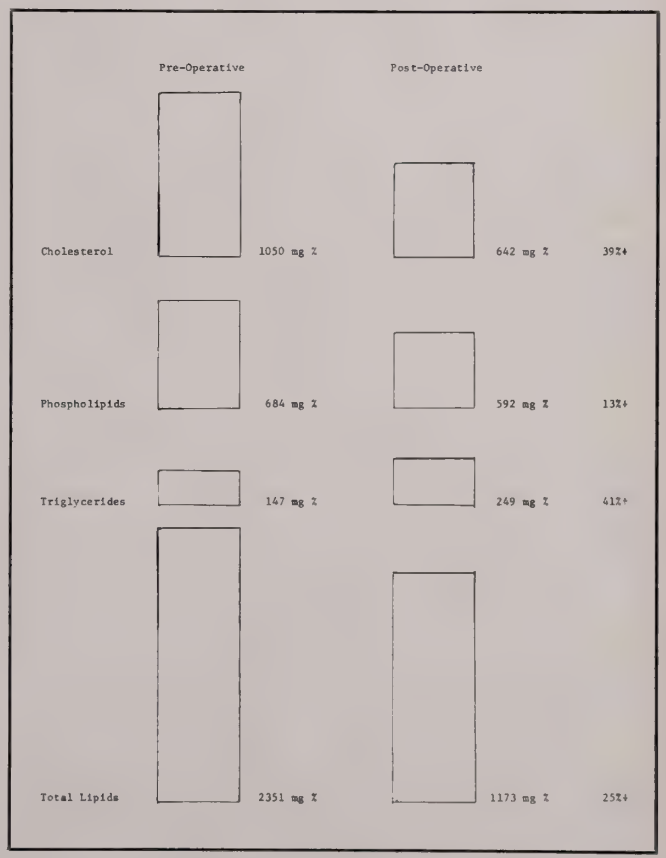


Fig. 5—Serum lipids before partial ileal bypass and six months thereafter.

after exercise.

Surgery

Subsequent to evaluation, the patient was scheduled for a partial ileal bypass operation. During induction he developed supraventricular tachycardia with a rate of 220 beats per minute and a rise in systolic pressure to 250 mm.Hg. The operation was cancelled. On awakening he had severe precordial chest pain radiating down his left arm which failed to respond to nitroglycerin and required morphine for its control. With digitalization, his rate converted to a regular sinus rhythm at 70 beats per minute. At this slow rate his chest pain ceased and his general condition improved. We treated the patient for the next week as if he had sustained a myocardial infarction, but serial enzyme patterns, electrocardiograms, and his clinical course failed to substantiate the diagnosis of acute myocardial necrosis. It was, nevertheless, deemed prudent to postpone an operation.

Two months later he was again taken to the operating room and once again an episode of tachycardia ensued despite adequate digitalization and careful anesthetic induction. This tachycardia cleared as the plane of anesthesia was deepened. Bypass of the distal 200 cm. of the small intestine was carried out from a total small intestinal length of 400 cm. He recovered uneventfully from this procedure.

Subsequent Course

The patient was re-evaluated six months postoperatively. His activity was essentially the same as prior to his operation, he had regained his previous weight, and his bowel pattern had returned to his preoperative one to two bowel movements daily. His blood hematology, coagulation, and electrolyte values were again normal. His serum uric acid had decreased to 5.5 mg%. His fasting blood sugar was 58 mg% and his two-hour post-prandial sugar 79 mg%. Total serum proteins were 6.6 mg% with an A/G ratio of 4.0/2.6. His serum calcium was 9.4 mg%, his serum phosphorus 5.0 mg%, and his serum magnesium 1.7 mg%. The serum carotine and serum vitamin A levels were within the normal range with values of 95 and 30 ngm%, respectively. The electrocardiogram was unchanged.

The serum cholesterol over a consecutive six-day period ranged between 711 mg% and 825 mg%, with an average value of 762 mg%; this is a reduction of 16% from the preoperative average of 908 mg% determined in our chemistry laboratory. Serum lipids, measured at the Bio-Science Laboratories, showed a serum cholesterol value of 642 mg%, serum phospholipids of 592 mg%, serum triglycerides of 249 mg%, and serum total lipids of 1773 mg%. Comparison of these values with the preoperative determinations is graphically shown in Figure 5, revealing a reduction in the serum cholesterol and in the serum total lipids; the serum phospholipids are only slightly reduced and the serum triglycerides are paradoxically elevated. The staining of the beta band on the lipoprotein electrophoretic pattern was diminished.

Though cholestyramine was unsuccessful preoperatively in lowering this patient's cholesterol level, we attempted six months after surgery a four-week trial with a daily dose of 32 grams of cholestyramine, but this regimen failed to reduce his cholesterol level further.

Discussion

Although hypercholesterolemia in the American population is common, familial hypercholesterolemia with well-documented xanthomatous lesions is uncommon, and the occurrence of the homozygous state of this disease is a rarity. If we are to manage a patient with this problem successfully, maximum therapy must be offered as soon as a diagnosis is made and, preferably, before progression to the advanced stage evident in this patient. Early detection is possible with the presence of xanthomatous lesions and an elevated serum cholesterol. Dietary therapy (low cholesterol, low saturated-fat diet), though somewhat effective in the so-called idiopathic hypercholesterolemic patient, is ineffective in the familial form of the disease. Neither do the hypocholesterolemic drugs currently available seem to benefit this type of patient. A moderate measure of success in this patient, as evidenced by the lowering of his serum cholesterol and serum total lipid concentrations, has been achieved by partial ileal bypass. Based on previous experience, we believe that the reduction in the cholesterol level will persist and may become greater. It will take the test of time and the performance of repeat arteriographic studies to ascertain whether the cholesterol reduction proves to be, in some measure, clinically beneficial to this young patient in arresting or retarding the progression of his disease.

Summary

A case report of a 14-year-old patient with severe coronary artery disease, aortic stenosis, aortic insufficiency, arcus senilis, vessel bruits, and diffuse peripheral xanthomatosis, associated with the homozygous form of type II familial hyperlipidemia has been presented. The patient was treated by partial ileal bypass operation, and serum cholesterol and serum total lipid levels were subsequently lowered.

Acknowledgments

We are indebted to Dr. Milton Paul, Director, Division of Cardiology, Willis J. Potts, Children's Heart Center, Chicago, for referring this patient and his family to us.

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It's the Law

Drug Manufacturer Not Liable for Intestinal Lesion

The patient developed abdominal pains after taking a drug (HydroDIURIL-Ka-50) for several months. An operation was performed, disclosing a nonspecific lesion in the small intestine. This lesion was removed.

The patient contended that the manufacturer was negligent in not having made more extensive tests before putting HydroDIURIL-Ka-50 on the market. A trial court properly determined that the manufacturer was not negligent in failing to make adequate tests before putting the drug on the market, in view of the long and medically approved use of potassium chloride and diuril separately.

Case Reference: "O'Hare v. Merck & Company," 381 F. 2d 286 (C. A. 8, July 19, 1967: rehearing denied, August 29, 1967). The Citation. 16:6, 1967.

DERIVATIVELY SPEAKING

Atelectasis—from Greek *ateles* (imperfect) plus *ektasis* (expansion)

WHAT'S YOUR DIAGNOSIS?

A 67-year-old white female was admitted to the hospital for evaluation of renal function in relationship to a persistent hypertension. She gave a history of persistent hypertension over several years, and blood pressure at various times was recorded as 200/100. She complained of an occasional "light-headed" feeling. She was also known to have a small hiatus hernia which occasionally caused some dysphagia. On admission her general physical examination was negative except for the noted hypertension and a suggestion of slight left ventricular cardiac enlargement. Pulse was 76 and regular. Electrocardiogram was normal. On her third hospital day she was required to drink four glasses of water for a renal function test. On finishing the fourth glass of water she became nauseated and vomited the water and a small amount of blood. She then began to have severe anterior chest pain radiating across the costal margins. The pain was persistent and became more severe. Examination later that same day revealed the patient to be complaining of severe pain in the left anterior lateral chest. She appeared ashen, but blood pressure was in the normal range. She was perspiring and in obvious distress. Subcutaneous air was palpable in the neck and there was a pleural rub heard over the left lower chest and a pericardial rub heard beneath the lower third of the sternum.

What's your diagnosis? (Turn to page 488).

Ebstein's Syndrome

Although some writers have referred to this condition as a syndrome, it is more commonly known as "Ebstein's malformation." It consists of : (1) a tricuspid valve deformity, resulting in marked dilatation of the right atrium; and (2) an impairment of action of the right ventricle, causing pulmonary arterial blood flow and underfilling of the lungs. Ebstein described this malformation almost 100 years ago. At least 71 cases were reported to 1953 (Kilby *et al.*).

The clinical picture is typical in most cases, but the effect of the aberration on function may vary considerably. Dyspnea and cyanosis may be present at birth or may appear later. The basic deformity follows the same pattern. The posterior leaflet is displaced downward and is adherent to the ventricular wall to a variable extent; the anterior leaflet often forms a long veil-like structure. Considerable variation occurs in the size of the right ventricular chamber and in the thickness of its wall.

Kilby and associates consider the picture complete if: (1) the electrocardiogram is characterized by a pattern simulating right bundle branch block, although the R wave from the right precordium is of low voltage and of a multiphasic type; (2) auscultation reveals a double murmur in the left parasternal region, with perhaps a loud third heart sound; and (3) x-ray shows moderate cardiac enlargement with decreased pulmonary vascular markings.

Angiocardiographic and phonocardiographic findings help to establish the diagnosis. Differential diagnosis should exclude the tetralogy of Fallot, tricuspid atresia, and pulmonary stenosis with interatrial defect. Five of the nine patients who were studied by catheterization at the Mayo Clinic were reported to be alive one to three years later (Kilby *et al.*). Surgical closure of a patent foramen ovale had been effected in one of these patients.

Durham, Robert H.—Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

Precancer and Cancer of the Skin*

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Minneapolis, Minnesota

PHYSICIANS ARE frequently confronted with differentiation between precancer and cancer of the skin and must make a decision as to biopsy, removal, and follow-up. Many of the lesions to be discussed have characteristics which can aid the physician in his management of these skin growths.

Pseudo-Carcinomatous Hyperplasias

Pseudoepitheliomatous Hyperplasia

In this condition there is a reactive thickening and proliferation of the skin which clinically or histologically may suggest carcinoma. It is found in association with stasis, ulcers, bromoderma, blastomycosis, granuloma inguinale, lupus vulgaris and other chronic processes. Histologically this proliferation may be difficult to differentiate from true carcinoma, and its presence does not rule out the possibility of true carcinomatous change occurring in any of the underlying chronic diseases. The value of its recognition lies in avoiding extensive procedures for a benign reactive condition, with treatment directed at the primary disease.

Keratoacanthoma

This tumor has been recognized with increasing frequency in localized and generalized forms. In the latter type, tumors occur in an eruptive nature in a generalized distribution and heal with scar formation. The disease is considered to have an hereditary basis. The localized variety occurs much more frequently and presents more difficulty. It begins as a papule and may reach 5 to 7 cm. in diameter (more commonly 1 to 2 cm.) in a matter of several months (Figure 1). Involution takes up to 12 months or more. When fully developed the keratoacanthoma is an erythematous to skin-colored nodule with a central crater filled with a keratin plug. Because of its close resemblance to squamous-cell carcino-

*Presented at the Continuation Center, University of Minnesota, October 19, 1967.

ma, surgical excision and histologic examination is the desired treatment .

Premalignant

The word premalignant is confusing, for some of the skin lesions under this heading may never turn malignant while others may already be cancerous. Not all premalignant lesions, such as actinic keratosis, need be removed. Periodic examinations are often sufficient, along with instruction to the patient to report growth or other change in the lesion.

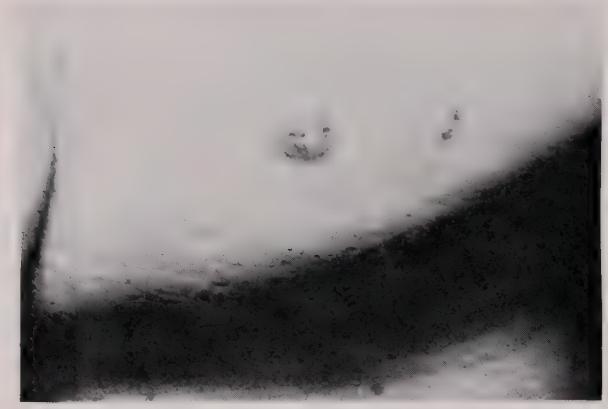


Fig. 1—Keratoacanthoma showing central keratin plug with surrounding elevated border.

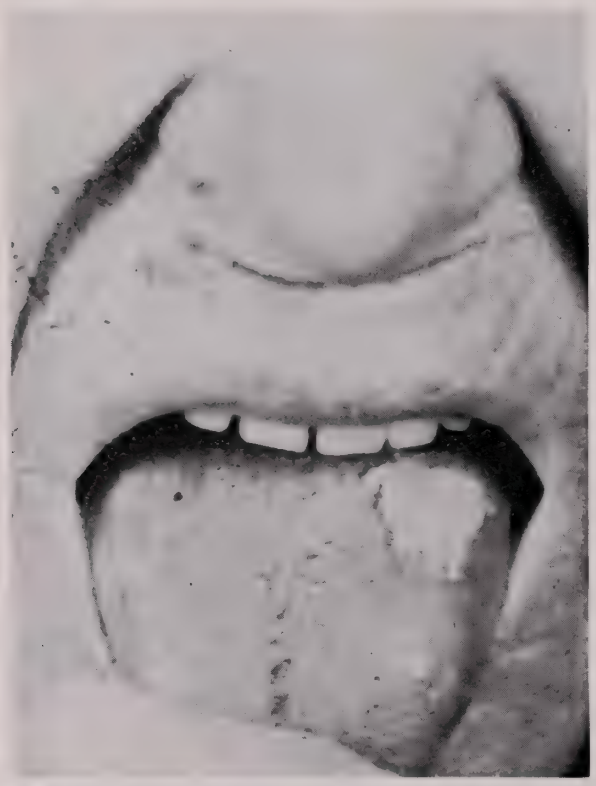


Fig. 2—Leukoplakia on the dorsal tongue with characteristic plaque-like appearance.

In actinic keratosis the patient should avoid any exciting factors, such as prolonged sun exposure.

Actinic Keratosis (Senile Keratosis and Cutaneous Horn)

These common lesions usually occur on exposed areas and in the latter decades of life. They may be single or multiple and occur more often in individuals who have undergone considerable sun exposure. Hereditary factors may also be involved, such as fair complexion. The lesions have a verrucous or scaly appearance, may be erythematous or pigmented, and occasionally can be detected only by palpation. Actinic keratoses generally occur on skin which shows other evidence of actinic changes. Squamous-cell carcinoma will appear in about 25% of these cases.

Treatment is usually surgical. Some individuals may have so many of these lesions that any of the surgical methods such as curettement, electrocautery or excision are impractical. In these cases, regular examinations with removal of those lesions showing growth or other changes may have to be the form of management.

Leukoplakia

This condition occurs on the mucous membranes, most notably the mouth, penis, and vulva. In the oral cavity, the lips, gums, cheeks and dorsal tongue are most frequently involved. On the penis, the glans and foreskin in uncircumcised older men are susceptible. The condition varies in both symptoms and appearance with the duration of involvement. At first there are no symptoms; later, burning and discomfort occur with minor irritation. The appearance is that of superficial patches of various shapes which may be glistening and in some areas even mildly pigmented. Later the lesions thicken and may become verrucous with fissures and ulceration. This condition may exist for years without malignant change; yet induration may begin insidiously around an inflamed area, ulcer, or fissure, with resulting carcinoma of an invasive nature (Figure 2). Treatment of the leukoplakia itself consists of removing any chronic irritations (e.g., carious teeth, poorly fitted dentures, smoking). In some cases following removal of an irritant the leukoplakia may

regress. Isolated areas may be treated with liquid nitrogen, electrocautery and, in extensive cases, plastic surgery. When carcinoma occurs, surgical excision is indicated.

Arsenical Keratoses.

Arsenic in the inorganic form may induce keratoses as well as basal and squamous-cell epitheliomas. The keratoses that occur following the ingestion of inorganic salts of arsenic are found with greatest frequency on the palms and soles. Elsewhere, Bowen's disease and basal-cell epitheliomas may occur. The interval between ingestion of arsenic and the development of the keratosis may vary from months to years. On the palms and soles the lesions are discrete keratotic growths somewhat resembling warts. At times they may become inflamed due to irritation. Malignant change occurs in approximately 20% of the cases. Treatment of this condition is unsatisfactory, because there are usually too many keratoses for surgical removal to be practical. Therefore, observation is used with frequent examinations for signs of malignant change. When this occurs excision is the preferred treatment.

Radiodermatitis.

This condition may be either acute or chronic. From the standpoint of potential malignancy, the chronic form is of most concern. Chronic radiation changes may occur following a known acute phase or may slowly make their appearance without this first stage. Clinically the skin in chronic radiodermatitis is dry, smooth, and atrophic. Telangiectasis and loss of hair may occur. In addition, there may be freckle-like spots or diffuse pigmentation as well as diffuse or spotty loss of pigment. If on the hands, the nails may become lusterless, brittle and discolored. Dystrophic changes of the nails may occur, such as ridging, splitting and delayed growth. With time keratoses may occur in these areas. These lesions are hard little plugs, brown to black in color, which may ulcerate with subsequent malignant change. When this occurs, the usual form of tumor is squamous-cell carcinoma. However, basal-cell epithelioma, sarcoma, and malignant melanoma have been recorded. In the treatment of mild chronic radiodermatitis various ointments may be used; however, with progressive or severe change, surgical methods such as grafting and excision of ulcers is of prime importance. Once malignant change has occurred, surgical excision, if feasible, is the indicated treatment.

Superficial Epithelioma

Lesions in this category are already carcinomas with the attendant potentials of this type of neoplasia and are therefore removed whenever diagnosed.

Bowen's Disease

This tumor is a specialized superficial epithelioma which clinically appears as an erythematous scaling plaque which may resemble psoriasis (Figure 3). Although there is usually no infiltration, ulceration may occur. Bowen's disease may be present on the exposed skin or on covered areas as well as on certain mucous membranes. When it is situated on the glans penis, vulva, or oral mucosa, the term erythroplasia (of Queyrat) is used. There appears to be an increased incidence of visceral cancer in individuals who have Bowen's disease, especially on the normally nonexposed areas.[1] This tumor may grow slowly, remain in situ for many years, and then transform to an invasive growth with metastasis. Treatment consists of curettement, electrocautery, or surgical excision, for these tumors are somewhat radioresistant.

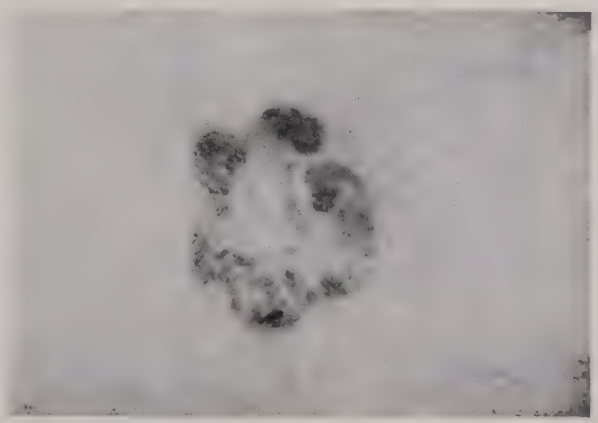


Fig. 3—Bowen's disease: note eczematous nature along with areas of early superficial ulceration.

Malignant

Neoplasia involving the skin shows a wide range of malignant potential. Basal-cell epitheliomas do not as a rule metastasize. In fact there appears to be increasing evidence that cu-

taneous squamous-cell carcinomas have a low rate of metastatic potential. On the other hand, melanomas may metastasize early and extensively before they are seen by the physician. Treatment of these lesions should be based upon the nature of the tumor and its clinical characteristics regarding growth and spread.

Basal-Cell Epithelioma.

Approximately 80 to 90 percent of all epitheliomas of the skin occur on the head and neck.[2] Basal-cell epithelioma occurs most frequently about the nose, eyelids and upper face. In most instances these tumors are single. However, some individuals have a greater tendency to develop these lesions and may have multiple tumors. Multiple basal-cell tumors may be seen after arsenic ingestion (Fowler's solution) as well as in the so-called basal-cell nevus syndrome.

The lesion may first be clinically evident as a small (1-2 mm.) erythematous macule or papule, gradually enlarging into a waxy nodule, which frequently shows fine telangiectatic vessels on its surface. With time, scaling, bleeding, crusting, and ulceration may occur (Figure 4). Even with ulceration and crusting the border of the lesion frequently maintains its waxy characteristic. In approximately 10 to 20 percent of these tumors, pigmentation may be present. Metastases are extremely rare with this tumor; however, when they do occur, the mortality rate is high. Treatment consists of biopsy of suspicious lesions; and if basal-cell epithelioma is shown to be present, excision, electrosurgery, radiation, or curettement may be used. The choice of modalities depends upon the size and location of the tumor as well as on the experience of the physician.

Squamous-Cell Carcinoma.

This tumor, like the basal-cell epithelioma, is more common on the head and neck in middle age and beyond. However, like the latter tumor it may be found anywhere on the body, especially the hands. The basal-cell epithelioma is more often found on the face about the nose, upper lip, eyelids, forehead, temple; whereas the squamous-cell carcinoma is more frequent on the lower lip and mucocutaneous junctions. However, it should be emphasized that this tumor may occur at any location where a basal-cell epithelioma can be found. The squamous-cell carcinoma usually begins as a scaling lesion and subsequently becomes infiltrated with a margin which may be rolled and hyperemic. The tumor may grow outward, inward, or both —with destructive ulceration occurring; there may also be extension into connective tissue, cartilage, periosteum and bone. In some instances metastatic extension occurs to the regional lymph nodes—more frequently with lesions on the hands (Figure 5). Early treatment of this tumor with surgical excision, curettement, radiation, or electrosurgery gives good results in experienced hands. Naturally, when deep infiltration has occurred or metastases are present, results are less favorable.

Malignant Melanoma

Of all skin tumors, nevi are the most prevalent. Young adults average about 40 benign nevi.[3] These lesions vary in size, color, and

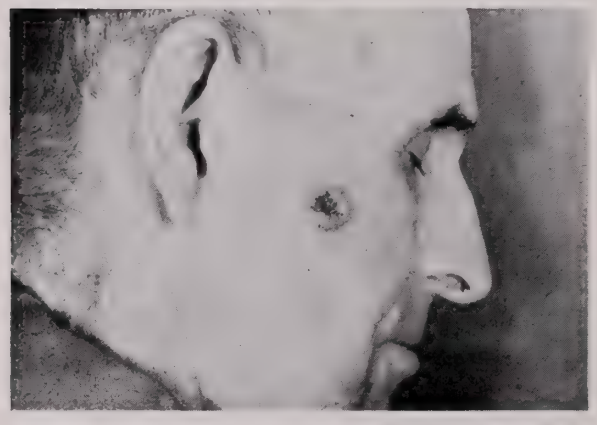


Fig. 4—Basal-cell epithelioma showing central area of crusting with surrounding wax-like border.



Fig. 5—Squamous-cell epithelioma on the dorsal hand with ulceration of its surface.

amount of pigment. Some are flat, others elevated. Nevi on the palms and soles are usually flat, pigmented lesions, histologically of a junctional nature. Malignant change may occur at any age; however, the sixth decade or beyond is the period of highest incidence. About 25 percent of melanomas arise from pre-existing benign nevi; in the remaining cases either the tumor has arisen de novo or the primary nevus cannot be found. Most of these pre-existing nevi are of the junctional type. This does not mean, however, that all junctional nevi are destined to undergo malignant change.

Melanomas which arise from a pre-existing nevus are to be differentiated from those referred to as lentigo maligna. This latter type occurs as a rule in older people and is a superficial, slow-growing tumor with a low grade of malignancy.

Melanomas vary in their clinical appearance. Some are flat, others elevated; they may be darkly pigmented or can in fact have little or no pigment present. With time the lesion usually ulcerates and becomes crusted. Metastases occur early with both local and systemic involvement, especially to the liver and lungs.

The physician is frequently confronted with the problem of removing benign nevi. It is generally accepted that nevi of the nail beds, growing nevi after childhood, those that are subjected to chronic irritation, and unusual or atypical nevi should be prophylactically removed. When a diagnosis of melanoma is made, the treatment is wide surgical removal, node dissection, and at times perfusion. Whether all these procedures will be employed is determined in each individual case.

Paget's Disease

Paget's disease as applied to cutaneous malignancy refers to a rare tumor which most frequently involves the areola and nipple in females; however, it may occur on or near the male or female genitals, the perineum and axilla. This lesion is usually erythematous, with scaling, oozing and crusting; and infiltration may be present. Clinically it can resemble Bowen's disease, psoriasis or simple eczema. When involvement of the breast occurs, retraction of the nipple may be present. Its origin is generally considered to be an intraductal or adenocarcinoma of one or more mammary ducts. The mammary glands being apocrine in nature have analogues in the other areas mentioned, which probably explains the extramammary occurrence. Treatment is surgical, the extent of the procedure depending on the site of the tumor.

Sarcomas

Sarcomas originating in the skin are rare. They are usually slow-growing and do not readily metastasize. With respect to the multiple idiopathic hemorrhagic sarcoma, this tumor probably has multiple foci of origin rather than metastatic spread from an original locus.

Dermatofibrosarcoma Protuberans

This tumor is a rare slow-growing connective-tissue tumor originating in the dermis. Clinically it may show either an indurated papule or plaque as well as multiple nodules. It is slow-growing and metastases occur infrequently, though it may be invasive. Histologically this lesion is composed of strands and whorls of collagen with only slight atypicality. Treatment is by surgical excision. This tumor is to be contrasted with the more malignant subcutaneous fibrosarcoma which usually arises in the deep subcutaneous layers of fascial tissue, grows rapidly and readily metastasizes.

Multiple Idiopathic Hemorrhagic Sarcoma (Kaposi's)

In this condition the patient shows an eruption of bluish-red papules, plaques and nodules (Figure 6). The most common location is distally on the lower extremities. It is more common in men. Visceral as well as lymph-



Fig. 6—Kaposi's sarcoma: note plaques, papules, and nodules.

node involvement is known to occur. Any organ may be involved, most commonly the gastrointestinal tract, liver, lungs, intra-abdominal lymph nodes and heart. The disease may be variable in its clinical behavior; some lesions may grow and ulcerate, while some may regress. As a rule the general course of the disease is protracted, with some cases having a course of 10 to 20 years or more. Death, when it occurs, may be due to internal hemorrhage, to intercurrent infection with debilitation, or to lymphoma of one type or another. Treatment is not satisfactory, though conservative use of fractional x-ray (filtered) may be employed as well as chemotherapy and cobalt infusions. Beyond this, supportive measures should be used.

Lymphomas and Myelosis*

Any of the myeloses may first manifest themselves clinically in the skin or involve the skin later in their course. As a rule the eruptions are nonspecific and resistant to therapy. In many instances it is this very resistance which leads to a skin biopsy and disclosure of the underlying disease. Within the lymphoma group, mycosis fungoides is of particular interest, for it may remain localized in the skin for many years and has a somewhat characteristic clinical course.

Mycosis Fungoides

This term is used to describe a rare disease which appears to fall within the broad category of lymphoma, manifesting itself first in the skin and following a fairly characteristic course. Mycosis fungoides may begin as a banal dermatitis, only to progress to a fatal, often protracted, termination. The disease is divided into three stages, although all three need not occur in the course of the condition. Also, the various stages may overlap, with some cases showing characteristics of all three stages at one time. At its onset, mycosis fungoides may appear as a nondescript eczematous eruption, though often it may be psoriasiform in nature. This initial stage may continue for a period of years, with the patient maintaining relatively good general health. Eventually the eruption becomes characterized by polymorphism, bizarre patterns and vivid coloration. Infiltration occurs gradually, leading to the so-called plaque stage. Ulceration may occur at this point. Still later the third stage occurs and is characterized by nodules and tumors, which may appear on pre-existing plaques or arise on previously non-involved skin. The tumors have a tendency to become deep necrotic ulcers. The prognosis in this condition is serious, though remissions do occur, and the course may be prolonged. Treatment in the past has consisted of roentgen therapy along with supportive measures. Recently several chemotherapeutic agents have been used, though as yet it is difficult to judge their relative efficacy.

Other

Several other forms of tumors found on the skin should be mentioned. These include the so-called benign or nevoid adnexal tumors such as sebaceous, apocrine, and eccrine neoplasms, which may remain benign or become malignant. Some of these tumors, such as syringomas, may be suspected clinically; however, many have no characteristics by which to diagnose them other than histologic examination following surgical removal.

*See Test Your Word Score Page 511.

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ANSWER TO WHAT'S YOUR DIAGNOSIS

(From page 482)

A left thoracotomy was performed one hour later and this revealed a ruptured esophagus with a two-centimeter laceration of the medial wall of the esophagus just above the diaphragm. The rent was repaired and the patient made an uneventful recovery.

Incarceration of Transvenous Pacemaker Electrode

Removal by Traction

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CARDIAC PACING by a transvenous electrode has extended this therapeutic modality to patients too ill for thoracotomy and epicardial electrode pacing. Thus the transvenous electrode is often used temporarily in rhythm disturbances due to myocardial infarction. The present development of demand impulse generators, which avoid the risk of competition stimulation with resultant ventricular arrhythmia and fibrillation, will greatly increase the usefulness of the transvenous electrode in the management of myocardial infarction.

Transvenous pacing has been beset with many complications. The following complications related to transvenous electrodes have been reported in the literature.[1-7] While improvement of the impulse generators may reduce their related complications materially, the problems of the transvenous electrodes remain.

Arrhythmias during insertion
Bleeding
Infection
Thrombophlebitis
Wound sepsis
Subacute bacterial endocarditis
Air embolization
Phrenic stimulation
Fracture of electrode
Erosion of the electrode through the skin
Perforation of the right ventricle
Displacement of the electrode with loss of pacing

The transvenous electrode is quickly incorporated into the right ventricle wall, first by mural thrombus formation which is soon converted to scar by fibroblastic ingrowth. The somewhat bulky one inch of flexible electrode leading to the distal platinum tip, designed to minimize the risk of ventricular perforation, allows the electrode to be held firmly in this fibrous tissue. This is desirable

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as displacement of the electrode with loss of pacing is prevented. However, when the need for electrode removal arises, difficulties result from the fixation.

The following case reports illustrate the problem of removal of the electrode.

Case Reports

Case 1

A 43-year-old male was admitted to St. Mary's Hospital, Minneapolis, on January 24, 1967, following the onset of substernal crushing pain. Initial electrocardiogram showed posterior myocardial infarction. On the fourth day, first degree and intermittent second degree heart block appeared, progressing to intermittent complete heart block with ventricular rate of 50 to 60 per minute. On the tenth hospital day, ventricular rate dropped to 30, and intravenous Isuprel was required to maintain adequate cardiac output. A transvenous pacemaker was implanted and 20 days later the patient was discharged from the hospital with the pacemaker functioning. After two weeks, the impulse generator was turned off by percutaneous needling of the unit as sinus rhythm had returned. He remained well.

Eighteen weeks after insertion, removal of the pacemaker was undertaken with local anesthesia. The impulse generator was removed from the anterior chest wall and the electrode exposed where it entered the jugular vein. The electrode could not be pulled from the heart. With heavy pull on the electrode, the electrocardiogram would show either bradycardia or ventricular tachycardia. It was elected to abandon removal of the full electrode and, accordingly, it was cut and the impulse generator removed from its pocket. Ten days later, infection developed about the remaining electrode with thrombosis of the left subclavian and jugular veins.

Coagulase-positive Staphylococcus aureus bacteremia developed. This was controlled with antibiotics, but the wound on the chest wall remained purulent. It was evident that the electrode should be removed. Hand traction was again unsuccessful. Repeatedly, the electrode could be pulled out of the vein and stretched for a distance of three or four inches, but ventricular tachycardia would ensue. Upon release of the electrode, it would retract into the jugular vein for the entire distance it had been withdrawn. Sustained traction well below the pull that produced ventricular arrhythmia was then arranged by attaching the end of the electrode to a cord leading to a half-pound weight suspended over a pulley at the end of the bed (Figure). Removal was accomplished in the course of a few minutes.

Case 2

A 31-year-old woman was admitted to North Memorial Hospital, Minneapolis, on July 17, 1967, with a history of sudden onset of episodes of syncope. The electrocardiogram showed complete heart block. A transvenous pacemaker electrode was introduced

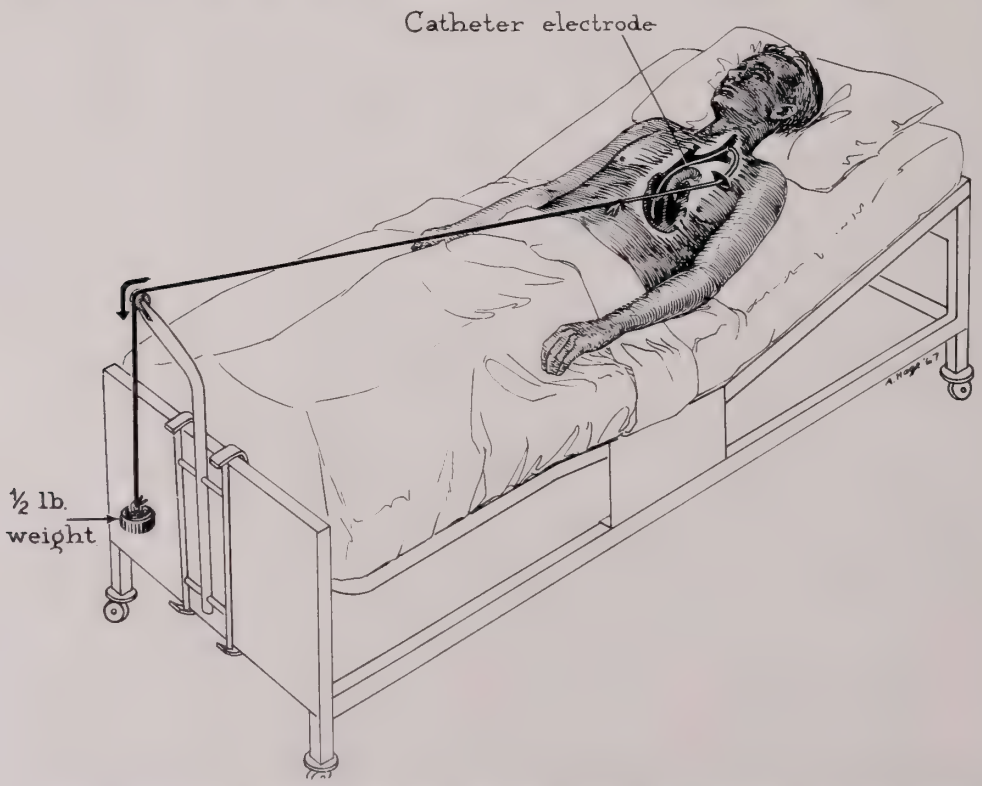


Figure: Diagram showing sustained traction applied for removal of incarcerated transvenous pacemaker electrode.

through the right saphenous vein and connected to an external pacemaker. Extensive studies failed to show the etiology of heart block. As her own rate never showed signs of returning to sinus rhythm, and because there was evidence of phlebitis developing in the right leg, on July 27, 1967, an epicardial fixed rate pacemaker was implanted through a thoracotomy. Attempted removal of the transvenous electrode after surgery met with resistance and it appeared that the electrode was incarcerated in the ventricle and/or along its course in the inferior vena cava and saphenous vein. Sustained traction was then applied to the end of the electrode over a pulley, utilizing a one-pound weight. The weight was gradually increased to a two-pound weight and in the course of a few minutes the removal of the catheter was accomplished.

Discussion

Review of the literature indicates that under similar circumstances others have pulled the electrode out of the vein as far as it would come without ventricular difficulties, then cut it off and let the remainder of the electrode retract into the vein. They have then resorted to cardiotomy* to remove the remainder of the electrode.[1,6,7] Gentle steady traction can also be utilized for removal of direct myocardial wires, inserted at time of surgery for other cardiac lesions, where temporary pacing is planned. It has been our experience that not infrequently such myocardial wires could not be completely removed, and we have had to be content with pulling the electrode out as far as it would come and cutting it off at this point, hoping the uncovered portion would not be troublesome.

*See Test Your Word Score Page 511.

Summary

A transvenous electrode may become densely adherent to the endocardium of the right ventricle and resist removal.

Adherent electrodes have been removed by gentle, steady traction in two such instances. This method may be worthy of trial before cardiotomy is undertaken to remove an incarcerated electrode.

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His Nganga* Failed

Musavengi:* a MuZezuru aged about forty. His father had died three years before and Musavengi had been ill for a year. When he first complained of a sore throat he had visited a diviner, whose hakata (divining bones) showed that his father's spirit wanted a bull to be named after it. The nganga's fee for the divination was five shillings. Musavengi named a bull after the spirit of his father and brewed the beer. He felt a little better after this, but his improvement was not maintained.**

*See Test Your Word Score Page 511.
**Michel Gelfand: Witch Doctor, 1965.

Reprisal

What sin did Miriam commit that she should be smitten with leprosy?

She had incensed the Lord by presuming to criticise Moses for having married an Ethiopian woman and for being one of God's favorites.

And the Lord came down in the pillar of the cloud, and stood in the door of the tabernacle, and called Aaron and Miriam: and they both came forth.

And the cloud departed from off the tabernacle; and, behold, Miriam became leprous, white as snow: and Aaron looked upon Miriam, and, behold, she was leprous. (Numbers 12:5, 10.)

YOUR HEALTH—MR. PRESIDENT!

William Henry Harrison (1773-1841)

The health record of our ninth President and nation builder, William Henry Harrison, contains only one sensational entry: narrow escape from death by a bullet. During Harrison's governorship of Indiana Territory a disgruntled Indian shot at him through a window while he sat in his home with Baby John in his arms. Fortunately neither the father, destined to become President, nor the infant son, destined to sire a President, was struck.

As child and man William Henry Harrison was of average health, neither robust nor frail, and enjoyed outdoor sports such as swimming, fishing, and especially horsemanship.

At the conclusion of a classical college course at Hampden Sydney, fertile soil for aspiring medical students, young Harrison began the study of medicine under Dr. Rush at the College of Physicians and Surgeons in Philadelphia. After only a few months, however, family funds ran too low for him to continue and he left Anatomical Hall to enter the army as an ensign destined to become the famous general and military strategist of We-have-met-the-enemy fame, with the sobriquet of Old Tippecanoe.

While actively engaged in the Indian Wars and the War of 1812 Harrison was laid low with army camp fever, Nature's insidious reprisal for logistic failure to provide adequate food, clothing, and shelter for the soldiers in the field. Before his recovery was complete he suffered a relapse due to overexertion while directing restoration on flood-damaged neighboring property.

Harrison was a naturally temperate man; but if his sobriety needed reinforcement, military life provided it. Of the mortality in the army due to alcoholism he said: "At least four fifths of my brother officers died from the effects of intoxication."

On Harrison's bone-chilling inauguration day, while he delivered his one-hour-and-forty-five-minute acceptance speech without hat or coat, he caught a severe cold. While convalescing he summoned his personal physician—not to prescribe for him but to discuss his several chronic ailments: neuralgia of the head and limbs; constipation, for which he swallowed an abundance of cathartics; and dyspepsia, for which he had himself ineffectually prescribed first a meat diet and then a starvation regimen. Nevertheless, the doctor did prescribe: relaxation and serenity plus cupping.

When only partially recovered from his cold Harrison rashly ventured forth one inclement day to do some marketing, the aftermath of which indiscretion was pneumonia, for the fever of which he deluged his system with water "to keep up his strength." His subsequent failure to improve brought in a team of five doctors who found that in addition to pneumonia their patient showed symptoms of intestinal inflammation and jaundice; whereupon they instituted a procedure of "topical depletion, blistering and appropriate internal remedies which subdued his lungs and liver," but not his stomach and intestines.

Treatment was of no avail. Old Tippecanoe died on April 4, 1841, after completing one month of his presidential term, the first United States President to die in office. The death report certified that "bilious pleurisy" was responsible for his demise. No autopsy was held. Had one been conducted, however, it would have failed to reveal any concrete evidence of the psychic ravages that constitute the price of high office and that historians agree must have contributed appreciably to Harrison's final dissolution.*

*With acknowledgments to Karl C. Wold, M.D.: Mr. President—How Is Your Health and to Freeman Cleaves: Old Tippecanoe.

Endotoxic Shock in Obstetrics and Gynecology*

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Shock is a condition of protean causes and manifestations. Among the latter, there is arterial hypotension and consequent inadequate perfusion of oxygenated blood to the body tissues. Such perfusion depends on three components: the circulating volume or blood, the vascular channels, and the pump or heart activating this ternary system. According to the component affected, several varieties of shock may ensue. Hypovolemic shock reflects loss of circulating volume either to the exterior or into internal body compartments. Cardiogenic shock indicates an impaired cardiopulmonary pump. Decreased peripheral resistance resulting from peripheral vasodilatation, while not invariable, may characterize the type of shock caused by bacterial toxins.

Bacteremic shock may complicate bacterial invasion of the bloodstream. A sustained, often precipitous decrease in systolic blood pressure to 80 mm of mercury or below is noted in a person previously normotensive, and bacteria are recovered from blood cultures obtained during or shortly preceding the hypotension.[1-4] Because blood pressure may not faithfully reflect the status of the microcirculation to various body organs, inadequate tissue perfusion may be present prior to the clinical detection of hypotension. Notwithstanding, sustained systemic arterial hypotension remains the essential clinical manifestation of bacteremic shock since more sensitive clinical methods of detection currently are unavailable.

A simple but not exact division of bacterial toxins is that of (1) exotoxins, as produced by strains of gram-positive cocci, and (2) endotoxins, as released by gram-negative bacilli or obtained after their autolysis. The more frequent toxin concerned in the genesis of bacteremic shock is the endotoxin of gram-negative bacilli. Endotoxin is a polymolecular phospholipid-polysaccharide-protein complex in which the polysaccharide provides antigenic specificity and the lipid fraction purveys toxicity. Endotoxic shock is that variant

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of bacteremic shock resulting from the activity of endotoxin subsequent to gram-negative bacillary invasion of the bloodstream. This complication occurs in 20 to 30% of patients having bacteremia due to gram-negative bacilli.

Portal of Entry

At the Mayo Clinic in a series of 303 patients with bacteremia due to gram-negative bacilli, there was a urinary portal of entry in about 50%.[5] The biliary tract was the portal in 10%, and the rest of the gastrointestinal tract in 15%. The female genital system was indicted in 5%. In another 5%, other sources such as skin, postoperative wounds, and the respiratory tract were responsible. In 15% a portal was not evident. In about 50%, bacteremia occurred after surgical or manipulative procedures; two thirds of the procedures were genitourinary and one third, gastrointestinal.

Endotoxic shock is the most frequently encountered variant of bacteremic shock in pregnant and gynecologic patients. In about 50%, it is associated with induced abortion.[6,7] In these patients, other predisposing conditions and therapies include pyelonephritis, manipulation of the urinary tract, ruptured membranes, pelvic abcess, chorioamnionitis, advanced neoplasms, and operative obstetric and gynecologic procedures.

Causative Microorganisms

Strains of *Escherichia coli* cause about one half of these infections; *E. coli* and *Klebsiella-Enterobacter* organisms, together, are causative in two thirds. In recent years, *Pseudomonas* has displaced *Proteus* as the next most common pathogen in some series. Less common pathogens include *Bacteroides*,[8] *Paracolobactrum*, and *Achromobacter*.

Physiologic and Pathologic Considerations

The pathogenesis of human endotoxic shock remains incompletely understood. As data accumulate, it becomes apparent that the complication is not the result of a single hemodynamic aberration; some patients have reduced cardiac output and normal or increased peripheral arterial resistance, whereas others have essentially normal cardiac output or one that is increased two to three times normal and reduced peripheral arterial resistance.[9] As a generalization, in the normovolemic patients early in shock, there is a high cardiac output and low peripheral resistance. Later in the process, reduced cardiac output may ensue. In contradistinction to these patients, those who are hypovolemic when endotoxic shock develops may have a low cardiac output and high peripheral resistance.

Endotoxin apparently acts indirectly on blood vessels through the medium of an unknown component in blood and induces tetany-like activity of the vascular beds near the arteriolar level.[10] Vasoconstriction predominates initially, but alternating vasodilatation of progressive duration eventuates in vascular atony. Consequently, when vascular capacity is thus increased, blood is sequestered therein and diminished amounts are returned to the heart. Incomplete cardiac filling may result in reduced cardiac output, more profound hypotension, and diminished arterial blood flow. As a result, there is inadequate perfusion of vital tissues and organs with oxygenated blood. The anoxia prevents normal cellular metabolism and anaerobic cellular reactions dominate, with formation of acid metabolites such as lactic acid and pyruvic acid to the point of metabolic acidosis. The anoxic cells may release excessive amounts of potassium, resulting in hyperkalemia. Increasing amino-acidemia may manifest the anoxic liver's inability to metabolize the increased load resulting from tissue breakdown.

In endotoxic shock, blood volume usually is adequate, but perfusion is ineffective because of peripheral pooling; and neither in experiments nor in humans is there evidence of adrenal failure, even when the subject is moribund.[11,12]

In human subjects to whom repeated intravenous injections of the endotoxin of *E. coli* have been given, clinical responses are progressively lessened. As tolerance increases among such volunteers, serum antibody titers and complement titers rise.[13]

Autopsy studies frequently do not reveal findings that might be considered specific or diagnostic of endotoxic shock. Lesions of the kidneys associated with renal insufficiency may include renal tubular necrosis due to shock, but in some cases, nephrotoxins such as certain

antibiotics might also be responsible. In a few cases there is a distinct lack of correlation between severe renal failure and morphologic alterations of the kidneys. To date Mayo Clinic investigators have not found evidence suggestive of the generalized Shwartzman phenomenon or unequivocal evidence of disseminated intravascular coagulation.[14]

Clinical Features

Usually there is prodromic* fever, followed by moderate hypotension and tachycardia; initially the patient is restless but alert and maintains a relatively good urinary output. If the etiologic factor is septic abortion, the patient has uterine and adnexal tenderness and purulent vaginal discharge. Recognition of the complication and its pertinent treatment at this stage usually lead to recovery. Later, due to extension of the infectious process and to failure of homeostatic mechanisms, hypotension may become severe and the patient may appear lethargic, cold, and pale. Weakening of the pulse, tachypnea, collapse of superficial veins, and oliguria may also be observed. Metabolic acidosis (perhaps largely due to lactic-acidemia),[15] semicoma, refractory hypotension, cyanosis, dilated and sluggish pupils, gallop rhythm, hypothermia, and anuria signal the terminal stage of the complication.

The prognosis largely depends on early recognition of the syndrome as well as early institution of pertinent treatment. In different series, mortality rates vary from about 30% to 80%; at the Mayo Clinic it has been 37%.[3] The prognosis is also related to the nature and severity of the initial lesion, the presence of underlying disease, previous therapy, and such complications as superinfection and metastatic infection.

Treatment

Management of bacteremic shock presumes close scrutiny of potential candidates, because prompt detection and treatment are essential to minimizing the mortality rate. Increases of temperature and pulse rate associated with decreases of blood pressure and urinary output in such patients dictate the need for obtainment of samples of blood for culture and consideration of the need for empiric antibacterial therapy if no other explanation is immediately forthcoming. If a pertinent, although empiric, antibacterial regimen is not employed, or not employed early in the infection, the essential problem is not being attacked and the likelihood of recovery is correspondingly reduced. Other supportive procedures are designed only to maintain the patient's life until antibacterial therapy can control the overwhelming infection that is the essential cause of the vascular collapse. Occurrence of the complication in the pregnant woman obviously entails additional considerations of therapy and its effect on the fetus.[16]

Antibacterial Therapy

In-vitro inhibition tests, and frequently results of blood cultures as well, are mainly of retrospective value in the management of bacteremia due to gram-negative bacilli, because antibacterial therapy is often begun empirically before such data are available. To postpone antibacterial therapy until the results of these tests are reported would mean a delay of 24 to 72 hours and an increased chance of mortality.

Empiric antibacterial therapy is initiated either on report of positive blood cultures or in cases where bacteremia is likely, when blood has been drawn for culture. In the past, a tetracycline combined with streptomycin, or alternatively, chloramphenicol and kanamycin, has been the regimen given most often under these circumstances at the Mayo Clinic. More recently we have been investigating the combined use of cephalothin and a polymyxin (polymyxin B and colistin) given under these circumstances. Other possible empiric regimens that may warrant investigation are cephalothin plus kanamycin and ampicillin given with kanamycin or a polymyxin.

There are disadvantages of empiric use of such combined antibiotic therapy. These include the dual depressive effect on the gram-negative elements of the flora, making superinfection more likely. However, periodic study of the sputum and stools during therapy may reveal any floral changes and impending superinfection. Streptomycin, kanamycin, the polymyxins, and perhaps cephalothin are possibly nephrotoxic; excepting cephalothin, these drugs may cause a curariform effect that may be manifested by cardiac arrest and respiratory depression. Streptomycin and kanamycin are oto-

*See Test Your Word Score Page 511.

toxic, but the latter is more likely to cause deafness. Chloramphenicol is hematotoxic. The polymyxins also may cause cerebellar ataxia and other neurologic complications. It appears unwise to employ drugs in combination, which share a significant toxic effect, since such use may enhance the likelihood of occurrence of such toxicity.

With the advent of newer drugs, there has been a reevaluation of the policy of the empiric use of combined antibiotic therapy. Use of a polymyxin has a disadvantage because *Proteus* and *Bacteroides organisms* are usually resistant to it. Kanamycin is inadequate as a single agent because a number of *Pseudomonas* and most *Bacteroides* organisms are insensitive to it. Ampicillin is inactive against most *Klebsiella-Enterobacter* organisms, most *Proteus* bacilli that are indole-positive, and *Pseudomonas* organisms. Cephalothin is not active against all *Klebsiella-Enterobacter* organisms, *Bacteroides*, and indole-positive *Proteus* bacilli and usually is inactive against *Pseudomonas*. To date, there is no single agent available that assures complete coverage against gram-negative bacillary infections.

Currently, when the patient's course is unsatisfactory and microbiologic data are reported, the empiric regimen may be replaced with a more pertinent drug, in keeping with results of tests of in-vitro bacterial susceptibility. Against *E. coli*, such drugs as ampicillin, cephalothin, or a polymyxin may be applicable. As a generalization, strains of *E. coli* are susceptible to streptomycin, the tetracyclines, and cephalothin in about 50% of cases; these bacilli are susceptible to ampicillin, kanamycin, the polymyxins, and chloramphenicol in 80% or more of cases. The same generalizations are applicable to *Klebsiella-Enterobacter* organisms except that only about 20% to 30% are susceptible to streptomycin and to the tetracyclines, 50% to 70% are susceptible to the polymyxins, and about 10% of these bacilli are susceptible to ampicillin.

Among other drugs, penicillin G, ampicillin, cephalothin, and novobiocin are active against the indole-negative *Proteus mirabilis*, which causes 80% to 90% of clinical infections due to *Proteus* organisms. Cephalothin is active in only about 10% to 20% of infections caused by indole-positive *Proteus* organisms, that is, *P. vulgaris*, *P. morganii*, and *P. rettgeri;* chloramphenicol also may be effective, but differences between in-vitro and in-vivo results are frequent with this drug against these organisms. Consequently, kanamycin may be the drug of choice against indole-positive organisms. Polymyxin B or colistin is used especially against *Pseudomonas* organisms. Despite the availability of the newer drugs, a tetracycline often is preferred in bacteremia due to *Bacteroides* organisms; chloramphenicol is also effective against these organisms; penicillin G and cephalothin may be active against certain strains of *Bacteroides*.

Supportive Therapy

Considerable controversy exists regarding ancillary management of these infections, but those measures that are frequently employed are mentioned at least for the sake of completeness.

Important among these measures is the management of fluid and electrolyte deficits. If hypovolemia is present, it should be corrected; however, overadministration of fluids, especially of saline, during oliguria can embarrass cardiac function and induce pulmonary edema. Replacement of blood may be required in such patients as those having uterine bleeding or underlying hematologic disease. Monitoring of central venous pressure indicates the competence of the heart to accept and expel a given volume of blood and may serve as a guide to volume repletion. Fluids can be cautiously given as long as the central venous pressure is low or normal, that is, 5 to 15 cm of water.

Antiacidotic measures are being investigated, and although acidosis can be corrected by infusion of sodium bicarbonate, levels of lactate in the blood appear to be uninfluenced unless peripheral circulation is improved concurrently.

Surgery may be required to eradicate a nidus of infection. As examples of this requirement, laparotomy may be necessary for a pelvic abscess, chorioamnionitis may compel induction of labor, and septic abortion may necessitate curettage and perhaps hysterectomy. One attempts to control the bacteremia before subjecting the patient to added stress, but sometimes bacteremia persists until an infected nidus is removed.

Vasoactive drugs have been used in an at-

tempt to restore circulating homeostasis, and thereby counter so-called irreversible shock, and to forestall renal ischemia and renal shutdown. There are two types of adrenergic receptors situated in the vascular system: alpha and beta. Alpha-adrenergic receptors mediate vasoconstrictor responses, whereas beta receptors mediate vasodilatation. Thus, levarterenol (Levophed) or norepinephrine and metaraminol (Aramine) cause vasoconstriction by stimulating alpha receptors in blood vessels and are referred to as alphamimetic drugs. These two drugs and angiotensin (Hypertensin) appear to be the vasopressor drugs that have been used most commonly in the recent past. Unlike levarterenol and metaraminol, the action of angiotension appears to be independent of adrenergic receptors.

Isoproterenol (Isuprel)[17] and mephentermine (Wyamine) cause vasodilatation by stimulating beta receptors and are referred to as betamimetic drugs. Phenoxybenzamine (Dibenzyline)[18-20] and phentolamine (Regitine) also cause vasodilatation, but by the mechanism of antagonizing vasoconstrictor effects; such alpha-adrenergic blockers (alpha-receptor blockers) are referred to as alphalytic drugs.

Proponents of the use of vasodilators in place of vasopressors point out that pallor, sweating, and tachycardia reflect vasoconstriction. They postulate that dilatation of blood vessels rather than their further constriction by vasopressors is required to relieve vascular pooling. Despite considerable discussion based on animal experimentation, there is a lack of data on the efficacy of vasodilators in the management of human victims of endotoxic shock.

A possible basis for the discrepancy in opinions regarding the use of vasopressors is that less than desirable results have been noted in patients whose state of shock has become profound before its recognition. Currently it is recommended that one initiate therapy with a vasopressor, but that if the patient does not respond to such management after a reasonable interval, use of a drug such as isoproterenol is to be considered. However, if endotoxic shock is not diagnosed early and adequate antibiotic therapy is not quickly initiated, no vasoactive treatment, vasopressor or vasodilator, will have optimal effect. It probably is unnecessary to raise the systolic blood pressure above 100 mm of mercury in a previously normotensive patient.

Oxygen therapy and hyperbaric oxygenation may be helpful in experimental animals, but the logic of their use in humans is disputed.

An airway is provided if necessary.

Digitalization is carried out only if the central venous pressure remains above 15 cm of water and particularly if other evidences of cardiac failure, such as pulmonary edema, are detected.

There are no exact data that elevating the foot of the patient's bed and applying an abdominal binder and leg bandages are of substantial benefit.

Hypothermia[21,22] may reduce the need for cellular oxygenation, but its exact application remains unclear.

Renal failure, which is partial or incipient, may be reversed by mannitol given intravenously. Hemodialysis has contributed to maintaining life and reducing morbidity during the oliguric phase of renal shutdown.

Use of analgesics, sedatives, and other depressants is best minimized.

Not all investigators advocate the routine use of adrenal glucocorticoids. A review of mortality rates in reported series wherein adrenal glucocorticoids were used has indicated that patients receiving them may have a higher mortality rate. Among objections to such therapy are impaired immune response, increased susceptibility to upper gastrointestinal bleeding, and fatal staphylococcal superinfection. It may be wiser to limit the administration of adrenal glucocorticoids in nonpharmacologic doses to those patients who had been receiving them before the occurrence of the infection.

The routine use of blood or its products is not advised, because in the usual case of endotoxic shock there appears to be no loss of blood, but rather the stagnation and faulty redistribution of blood. It would not appear wise to chance overloading an already distressed vascular system. However, recent hemodynamic studies indicate the need for some revision of the concept that blood volume should be expanded only to replace obvious losses. Shock may respond well to volume expansion when there is no demonstrable site for blood or plasma loss. Such functional deficits in blood volume are presumably related to intravascular or extravascular sequestration.[9]

A rapid intravenous infusion of low molecular weight dextran, in patients with a normal central venous pressure but low cardiac output and hypotension, appears to be relatively safe and may restore the circulatory dynamics without resorting to a vasopressor or a vasodilator.[23] Dextran-40 has only recently become commercially available in the United States.

Heparinization to counteract intravascular coagulation has been advocated, but its benefit lacks clinical confirmation. Numerous other regimens, including sympathetic block, alpha-aminocaproic acid, testosterone, aldosterone, serotonin antagonists, chlorpromazine, and even antihistaminics, have been described as being helpful in experimental animals, but this does not automatically assure their efficacy in the human subject.

Comment and Conclusions

The outcome is considerably determined by the severity of the underlying infection and the duration of shock before institution of appropriate management. Patients who recover usually have had the benefit of early diagnosis and treatment. To assure the best prognosis, potential candidates must be recognized and managed accordingly. Along with monitoring of the candidate's temperature and pulse rate, hourly determinations of the blood pressure and recording of the urinary output appear to be the best routine objective indices of the patient's current status. It is our experience, that when shock has become advanced, optimal response to therapy is less likely.

Empiric antibiotic therapy is begun when report of cultures is received or, in seriously ill patients, after blood has been drawn for cultures. If the patient's condition and microbiologic data later indicate that such empiric therapy is unsatisfactory, it is modified accordingly. Use of specific antibiotics in the initial management of bacteremia due to gram-negative bacilli is only theoretically possible, because one is often thwarted by lack of cultural proof of the pathogen and almost always of its [in-vitro] susceptibilities. However, these difficulties are not so great that adequate antibiotic therapy cannot be devised on an empiric basis. If such a regimen is not employed, or not employed early in the infection, the essential problem is not being attacked and recovery is unlikely. Supportive therapy is designed only to maintain the patient's life until antibiotic therapy can control the overwhelming infection which is the essential cause of the vascular collapse.

To the present, most patients at the Mayo Clinic with endotoxic shock have received a vasopressor and antibiotic therapy; they have not received adrenal glucocorticoids. At the same time, evaluation and modification of the regimen are made; these include assessment of isoproterenol (Isuprel) as an antihypotensive drug and the rapid infusion of dextran in place of a vasoactive drug in selected patients.

Although pertinent antibiotic therapy and reasonable supportive measures can improve the survival rate among victims of endotoxic shock, certain sequelae of the infection can occur. Chávez Castro and his co-workers[24] have commented on these, including those related to fertility, menstrual abnormalities, and those that may complicate future pregnancies, such as abnormal implantation of the placenta, ectopic pregnancy, and uterine rupture.

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(1) Bilbao, M. K.; Frische, L. H.; Rösch, J., and Dotter, C. T.: Hypotonic Duodenography, Scientific Exhibit, Radiological Society of North America, Chicago, Nov. 27–Dec. 2, 1966.

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Editorials

Irradiation and the Fetus*

OVER THE PAST 20 years there has been an increasing awareness of the hazards of radiation. In an article in the August 1967* issue the reader's attention is focused on the value of diagnostic radiologic procedures compared to the potential damage to maternal and fetal gonads and hence to generations as yet unborn. Although the reader quickly senses that this problem is a complex one, the author's summary of the currently available data provides sufficient background information to allow the radiologist and obstetrician to weigh the potential risks of radiation exposure during pregnancy with the value of the proposed procedure. In this comparison, however, the reader should consider the roentgen exposures shown in the tables as maximum, because some of these data were collected without an attempt to reduce radiation doses to the absolute minimum.

The author discusses the radiological procedures used in two common obstetrical problems—cephalopelvic disproportion and placental localization. He recommends the replacement of older diagnostic radiation techniques still widely used in these two problems with modified or newer approaches that reduce radiation exposure of the maternal and fetal gonads without sacrifice of accuracy. At the present time x-ray pelvimetry offers the only method by which cephalopelvic disproportion can be accurately assessed. Although many techniques have been described for measuring the pelvis, the exposure of the maternal and fetal gonads and fetal total body radiation from x-ray pelvimetry remain significant. Exposure can be reduced not only by reduction of views from four or three to two as the author suggests, but also by the employment of other refinements of radiation technique such as proper coning, filtration of the beam, proper positioning of the patient to minimize the need for repeat films, the use of high kilovoltage, high speed screens and films, long tube to film distance and rapid developing solutions. All of these measures further reduce the radiation needed for quality radiographs.

The value of placentography in the management of suspected placenta previa is probably greatly overrated. No technique yet described is 100% accurate. Unlike cephalopelvic disproportion most suspected cases of placenta previa can be managed adequately without maternal or fetal exposure to radiation. If fetal maturity has been reached when the problem presents itself, direct digital examination for the placenta is the preferred method of diagnosis. This examination is done with facilities ready for abdominal delivery if immediate interference is necessary. If the infant is of premature size, expectant treatment is followed. It is academic to locate the placenta by radiologic means, because the expectant management of the problem is not altered. If

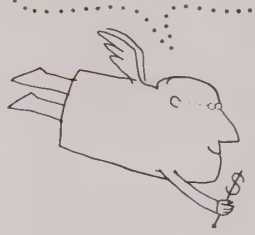
*Weisberg, M. G. Irradiation and the Fetus. Minnesota Med 50:1235, 1967.

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the clinician believes that exact location of the placenta is important, radiation exposure of mother and fetus is drastically reduced by the relatively new and fairly accurate technetium Tc99m serum albumin technique.

Clinical judgment and the use of non-radiologic means now available to the clinician, such as amniocentesis, determination of maternal urinary estriol excretion, fetal electrocardiography and ultrasound, have reduced or eliminated the need for radiologic techniques in the evaluation of some of the other clinical obstetrical problems mentioned but not discussed in the article, such as fetal maturity, excessive uterine enlargment, and suspected fetal death.

Non-obstetric radiologic diagnostic procedures during pregnancy are permissible if clearly indicated. The uterus and fetus can be shielded from direct radiation and the number of films can be reduced. Unintentional significant irradiation of the early pregnant uterus during the critical time of organogenesis can be prevented if all radiological examinations are done within 10 days after onset of a normal menstrual period or time is taken by the radiologist to ask appropriate questions and by the clinician to perform necessary examinations to eliminate the possibility of early pregnancy.

Konald Prem, M.D.
Minneapolis, Minnesota

Implantable Cardiac Pacemakers

ATRIOVENTRICULAR DISSOCIATION (heart block) disrupts the reflex pumping function of the ventricle with secondary results of heart failure, Stokes-Adams syndrome, and often death. Other than those surgically induced, most heart blocks follow a major or minor coronary artery occlusion. The monitoring experience of coronary care units indicates that many heart blocks are transient episodes of partial to complete atrioventricular dissociation interspersed with other cardiac rhythms. Unfortunately a single episode may result in cerebral anoxia and death.

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The subcutaneous unit does not impair physical activity, bathing, etc. and is stable for two to three years before a battery change is needed. Availability is nationwide. Every patient with transient or complete heart block should be carefully evaluated for such electronic help.

Jerome T. Grismer, M.D.
Reuben Berman, M.D.
Minneapolis, Minnesota

*Hannon, D. W., Connolly, C. J. and Edwards, J. E.: Complete Heart Block. Minnesota Med 50:1791, 1967.



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Diagnostic Use of Liver Biopsy

Doctors Knutson and Miller* have stressed the ease and safety with which the Menghini technique of needle biopsy of the liver was accomplished by "inexperienced physicians" in 59 patients. Without necessarily taking exception to their conclusions, I think that the implications of their report warrant comment, and some closely related considerations deserve emphasis.

The authors stated that utilization of diagnostic liver biopsy has been limited because of the skill required and because of the significant morbidity with use of the Vim Silverman needle. Other factors being nearly equal, if morbidity and mortality can be reduced by using the Menghini technique, then this method certainly would be preferable. The main disadvantage attributed to the Menghini needle is a relatively high failure rate in obtaining tissue from fibrotic livers. However, as yet, controlled studies of the relative merits of the two procedures have not been reported.

If, in fact, utilization of liver biopsy has been limited, this is perhaps more likely (certainly more ideally) to be related to a better general understanding of the indications, contraindications, and limitations of interpretation of liver biopsy.[1] These latter considerations are clearly more important to stress to inexperienced physicians than the relative ease with which the procedure can be performed.

Among patients with liver disease, biopsy of the liver is helpful for diagnosis in a relatively small proportion of cases. With intelligent selection of patients and critical use of the procedure, it is indeed simple, safe, and reasonably accurate with *either* the Menghini or the Vim Silverman technique.[2] More important than the type of needle is the experience of the operator and his familiarity with the technique he is using. The diagnostic success reported in any series depends primarily on the indications for which the procedure was employed and the experience of the pathologist interpreting the morphology of the specimens.

Leslie J. Schoenfield, M.D.

Rochester, Minnesota

*Knutson, D. D., and Miller, W. R.: Needle Biopsy of the Liver. A Five-Year Survey of the Menghini Technic. Minnesota Med 50:1627, 1967.

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The Cytologic Detection of Preclinical Carcinoma of the Uterine Cervix

During the past 20 years the cytologic detection of preclinical carcinoma of the uterine cervix through the routine use of cervical smear techniques has become a well-established laboratory procedure. This method of cancer detection, when first introduced, was not readily accepted by the pathologist or the clinician as a reliable or practical method of screening large numbers of asymptomatic women. However, once the pathologist became convinced of its value and the "modus operandi" was established, most clinicians were quick to seek out laboratories that offered this service. This fact is well substantiated by figures given in an article appearing in the January issue of Minnesota Medicine.* It is indeed creditable that 99 physicians from 28 regional centers in and around Duluth are screening nearly 12,000 women each year.

The numerical method of expressing the findings in a smear is fairly well standardized from laboratory to laboratory, but it is im-

*Wells, A. H., Kundel, D. W., Helwig, K. L., Michaelis, D. L., and Goldschmidt, V. G.: Smears from the Cervix: Cancer Cell Detection. Minnesota Med 51:25, 1968.

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1. Bradley, J. E., *et al.*: J. Pediat. *38*:41 (Jan.) 1951.
2. Bradley, J. E.: Mod. Med. *20*:71 (Oct. 15) 1952.
3. Crunden, A. B., Jr., and Davis, W. A.: Am. J. Obst. & Gynec. *65*:311 (Feb.) 1953.



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portant that a clear understanding exist between clinician and pathologist with regard to the significance of this method of reporting. Over the years, at the Mayo Clinic, about 50% of the class III smears have revealed carcinoma. Class II smears are rarely reported, and when they are it is because of extenuating circumstances or a situation in which the patient is easily accessible for a follow-up smear in order to detect the possible appearance of cells that in our opinion warrant tissue diagnosis. Individual interpretation of cell characteristics varies, so that some observers might choose to consider some of our class III smears as class II and recommend that repeat smears be taken at given intervals to determine whether or not progressive changes in the exfoliated cells make tissue diagnosis advisable. More than 90% of our cases in which a class III smear failed to reveal carcinoma in the cervical-cone biopsy showed varied degrees of epithelial dysplasia. Such dysplasia, in our opinion, is foreboding and should be eradicated as a preventive measure. The fact that over 40% of the carcinomas discovered in our laboratory were detected on class III smears serves to emphasize the close association of epithelial dysplasia and carcinoma, rather than a "hedge" by the pathologist in diagnosis. Extensive involvement of the junctional zone with carcinoma almost always yields a class IV or V smear.

As is stated elsewhere in this issue, the smear has no role in diagnosis of clinically obvious carcinoma of the cervix. In this situation, primary biopsy is the procedure of choice. In lesions of borderline significance, however, the smear may complement the biopsy, since occasionally the smear will reveal a carcinoma that has been missed at biopsy—even by an experienced examiner. Cauterization of the cervix should be delayed until after negative results of smear and biopsy have been received, since there is a risk of having the results of the cytologic study positive and having a patient with a partially denuded cervix that is not suitable for a reliable cone biopsy. Preclinical invasive carcinoma (microinvasive) has been found in about 10% of carcinomas detected by smear. This figure varies from one laboratory to another because individual interpretation varies in difficult cases involving borderline decisions.

The use of cervical conization as a therapeutic measure as well as a diagnostic tool is debatable. In those situations wherein excised cones can be immediately processed by reliable fresh-frozen sections to assure that the apex and base of the cone are free of carcinoma and it is assured that the patient will submit to a careful follow-up program, there should be no objection to employing conization in such a dual role.

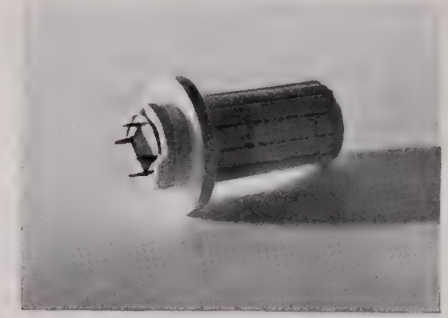
When in-situ carcinoma of the cervix is treated, three important facts must be remembered. (1) Extension of in-situ carcinoma onto the vaginal cuff occurs in a significant number of women. (2) In-situ carcinoma in 1 to 2% of affected women is multicentric in origin on the cervix or the cervix and vagina. (3) There is a tendency for the late occurrence of vaginal or even vulval carcinoma in women who at one time had in-situ carcinoma of the uterine cervix. Routine examination and vaginal smears then are mandatory, probably for the rest of the patient's life, irrespective of conization or simple hysterectomy as a mode of treatment. In addition, the age of the patient with respect to childbearing and the possible need for pelvic reparative surgery probably should be considered.

Excessive cost of case discovery has long been a "selling point" of those opposed to routine screening of asymptomatic women. For those women whose cancers have been discovered by smear, especially those with early invasion, this line of reasoning seems a little incredulous, particularly in light of the great sums being expended on esoteric medical research. The $787 expended in the Duluth area for the detection of a single carcinoma would appear to be money well spent. As the number of women in whom yearly smears are taken increases, the case-discovery costs may conceivably show an upward trend because, as the repeat smear population grows, the overall detection rate will diminish. However, with ever-increasing numbers of women being screened, the cost base broadens and the individual "insurance rate" remains the same.

Edward H. Soule, M.D.
Rochester, Minnesota

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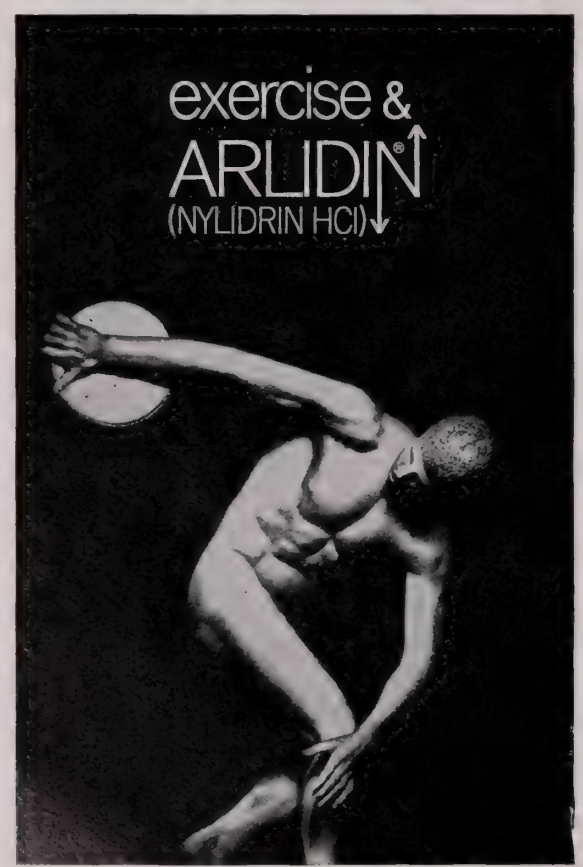


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Hostile Dependency in Marriage

WHY DO TWO people marry each other? All too often the answer is a mix of neurotic needs —complementing each other's unconscious, unresolved conflicts. Of course, many such marriages end in divorce, but more often the very factors that attracted the partners to each other hold the marriage together. The problems take many forms, but emotional immaturity almost always is a factor. Associated with such immaturity is a selfish, demanding, and pathologically dependent person. Hypertrophied dependency needs, a residuum of frustrated needs from childhood, suffocate the mutual give-and-take that a resilient, healthy, intimate relationship entails. With the inevitable development of problems in marriage, often accentuated by the demands put upon an emotionally immature woman with a growing family, old neurotic defenses tend to falter and new ones arise. The loss of self-esteem, the giving up of ideals of what marriage previously was believed to offer, a breakdown in communication between the partners, and the development of physical symptoms and bodily changes which bring about a realization of aging with a loss of vitality often result in frustration, bitterness, and anger which is either internalized or projected with resultant depression or paranoid ideation. Suspicions of the husband replace angry tirades involving the wife's own inabilities and eventually drive the couple to the point of no return with wounds that refuse to heal. Carter* has described this "paranoid wife syndrome" quite well.

When the physician sees such an angry, hostilely dependent woman with somatic symptoms, who also may have evidence of depression and paranoid ideation**, it is important that the evaluation also include the husband. Nothing can replace a thorough evaluation of the problem from all aspects in order to make the best effort toward resolution of the situation.

Therapeutic endeavors can be quite frustrating to the physician, especially when a hostile-dependent relationship is transferred to the doctor. Such problems must be handled individually, and as Dr. Carter has pointed out, multiple solutions can be effected; but it is important to realize that the physician, who often is caught between the spouses in the marital struggle, must remain objective and point out possible solutions without being judgmental or an advice-giver.

Maurice J. Martin, M.D.
Rochester, Minnesota

*Carter, D. C.: Paranoid Wife Syndrome. Minnesota Med 51:307, 1968.

**See Test Your Word Score below.

Test Your Word Score

Homozygous—*producing germ cells that transmit identical genes* (page 477).

Myelosis—*abnormal proliferation of tissue* (page 488).

Cardiotomy—*incision into the heart wall* (page 491).

Nganga—*Southern Rhodesian witch doctor* (page 491).

Musavengi—*was admitted to a Southern Rhodesian hospital after his nganga failed to cure him* (page 491).

Prodromic—*premonitory of a disease* (page 495).

Ideation—*forming ideas* (above).

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The Editor's Soliloquy

Paul Revere Bowl—The St. Barnabas Bowl

"Listen my children and you shall hear
Of the midnight ride of Paul Revere."

That famous ride made Paul Revere immortal in national legendary. In the American imagination he still gallops on the road to Lexington.

But as a product of our Revolutionary era he was far more than patriot: instigator of resistance and communal speaker for independence. He was, in addition, one of the most ingenious and versatile craftsman this country can point to with pride and distinction. His innate and irresistible creativity demanding expression doubtless contributed to Revere's phenomenal achievement.

Within the field of medicine Revere's notable civic activities included the Presidency of Boston's first Board of Health and the office of Coroner for Suffolk County, and though he demonstrated no other talent in the field of medicine or surgery his early cognizance of the deplorable condition of Bostonians' teeth induced him to practice restoration dentistry for a while. Appearing in the Boston Gazette his advertisement claimed: "He has fixed some Hundred of Teeth and he can fix them as well as any Surgeon-Dentist who ever came from London, he fixes them in such a Manner that they are not only an Ornament, but of real use in Speaking and Eating; He cleanses the Teeth and will wait on any Gentleman or Lady at their Lodgings, he may be spoke with at his Shop, where the Gold and Silver smith's Business is carried on in all its Branches." However, Revere soon lost interest in improving defective dentition and abandoned the field, despite its lucrative prospects.

After the war Revere conducted a retail business in his shop; with Yankee shrewdness he realized that a nice profit could accrue from importing and selling articles that were scarce in Boston: hardware, paper products, Sheffield plate, drygoods and notions, and eyeglasses. He was also co-founder and president of the Massachusetts Charitable Mechanics Association and one of the original incorporators of the Massachusetts Fire Insurance Company.

As metallurgist Revere pioneered and innovated in such substances as iron, copper, gold, and particularly silver. In his own mill he produced copper fittings for boats and ships and, subsequently, copper sheathing for their hulls. The Constitution, the Essex, and over twenty other ships were assembled with copper fastenings from the Revere mill; and later Old Ironsides received a new copper hull from the same mill.

Then there were bells! Where Revere mastered the principles of such a technical process as bell casting—with its esoteric secrets of assaying and moulding—remains a mystery. Of the Revere output there remain extant in New England today some 75 fine bells, unimpaired in structural and tonal excellence and beauty. Incidentally, the bell of the Constitution, shot away in action, was a Revere product.

Above all, Revere was a paragon in silversmithing, the craft he had learned from his father. Under his magic touch there materialized chafing-dishes, urns, coffee and tea pots, pitchers, porringers, and bowls—all functional in design and pre-eminent for their elemental strength, simple dignity, intrinsic symmetry, and exquisite luster.

Designed on the lines of Chinese porcelain bowls, Rever's Liberty bowl, one

of his handsomest pieces, was a gallon-capacity punch bowl fashioned in honor of the seventeen members of the Massachusetts General Court who voted not to rescind the circular letter sent to the other colonies in opposition to the Townshend duties on imports.

Many of the finest examples of Revere's craftsmanship in silver are exhibited in the Boston Museum of Fine Arts—to astonish and captivate the eye and mind of the beholder.

Can you now understand why I feel so humbly thrilled and honored to have received the sterling silver replica of Paul Revere's Liberty Bowl: the Saint Barnabas Bowl! From the bottom of my heart, I thank you.

—Carl O. Rice, M.D.

Old Doc Hess says: That man has the power of a famous name.—C.O.R.

Remedies Derived from the Hippopotamus

The hide, reduced to ashes and applied with water, is curative of inflamed tumours, and the fat, as well as the dung, used as a fumigation, is employed for the cure of cold agues. With the teeth of the left side of the jaw, the gums are scarified for the cure of tooth-ache. The skin of the left side of the forehead, attached to the groin, acts as an antaphrodisiac; and an application of the ashes of the same part will cause the hair to grow when lost through alopecy. The testes are taken in water, in doses of one drachma, for the cure of injuries inflicted by serpents.—Pliny

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Minnesota Medicine Cover Photographs

In order to encourage more physicians to submit color slides for use on the cover of MINNESOTA MEDICINE the competition is being discontinued. The picture editor now invites all physician-photographers to send 35 mm. color slides of suitable subjects for consideration as cover pictures. The format must be horizontal because of printing limitations. Pictures high-lighting Minnesota seasons, places, and activities will have an automatic advantage. No limit as to the number of slides sent will be set, but all slides should be individually identified. All slides will be returned. Physicians whose pictures are used as covers will be recognized in MINNESOTA MEDICINE. We can use many more pictures than we have received in the past.

Therapy

A good laugh and a long sleep are the best cures in the doctor's book.—Irish proverb

---

Speech

Every man is born with the faculty of reason and the faculty of speech, but why should he be able to speak before he has anything to say?—Benjamin Whichcote

---

Statistics

A statistician is a man who draws a mathematically precise line from an unwarranted assumption to a foregone conclusion.—Jacob Braude: Speaker's Encyclopedia

---

When I was a boy I was told that anybody could become President; I'm beginning to believe it.—Clarence Darrow



Curbstone Consultation

Babinski Reflex

QUESTION: Is it possible to fake a Babinski reflex?

ANSWER: It is possible for a person who is familiar with the details of a Babinski reflex to produce a false positive result providing that he can overcome the withdrawal reflex.

Diphtheria-Tetanus

QUESTION: What is the route for giving diphtheria-tetanus combined to individuals after the age of 40 years?

ANSWER: Diptheria-tetanus toxoids combined is available in a special preparation for adult use and is given intra-muscularly. The recommended schedule consists of two injections of 0.5 c.c., one to six months apart, followed by a booster injection every five years.

Heart Attacks

QUESTION: Can persons who have had heart attacks return to moderately hard work?

ANSWER: About two-thirds of all patients who have had a heart attack are able to go back to their original degree of physical activity — or to a schedule a little below. Nevertheless, it is inadvisable to allow any person who has had a heart attack to return to an extremely strenuous occupation — anything for instance, that requires heavy lifting, straining or a great deal of hurry.

It is interesting to note that much has been learned about energy requirements of different types of occupations. Many of the positions that were formerly considered to have great energy requirements have been found to be much less demanding than originally thought. Nowadays, many factory workers spend much less energy per day than the average housewife.

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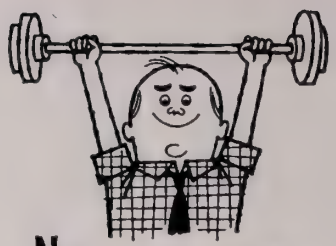
• Elemental Iron (as Ferrous Fumarate)	100 mg
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Vitamin B_2	7.5 mg
Vitamin B_6	7.5 mg
Vitamin B_{12}	50 mcgm
Vitamin C	200 mg
Niacinamide	30 mg
Folic Acid	0.05 mg
Pantothenic Acid	15 mg

Bottles of 60

* anticostive, *adj.* (*anti* opposed to + *costive* causing constipation.) Against constipation. (Now isn't that a good idea in an iron-containing hematinic? We'll send you samples if you'll send a request on your Rx blank, addressed to Department 150.)

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No matter how well you feel

there are two things you should do about cancer: Have a health checkup every year. Learn Cancer's Seven Danger Signals: **1.** Unusual bleeding or discharge. **2.** A lump or thickening in the breast or elsewhere. **3.** A sore that does not heal. **4.** Change in bowel or bladder habits. **5.** Hoarseness or cough. **6.** Indigestion or difficulty in swallowing. **7.** Change in a wart or mole.

If your signal lasts longer than two weeks, see your doctor without delay.

AMERICAN CANCER SOCIETY

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The Viewing Box

Dysphagia and Substernal Pain in a 62-Year-Old Man

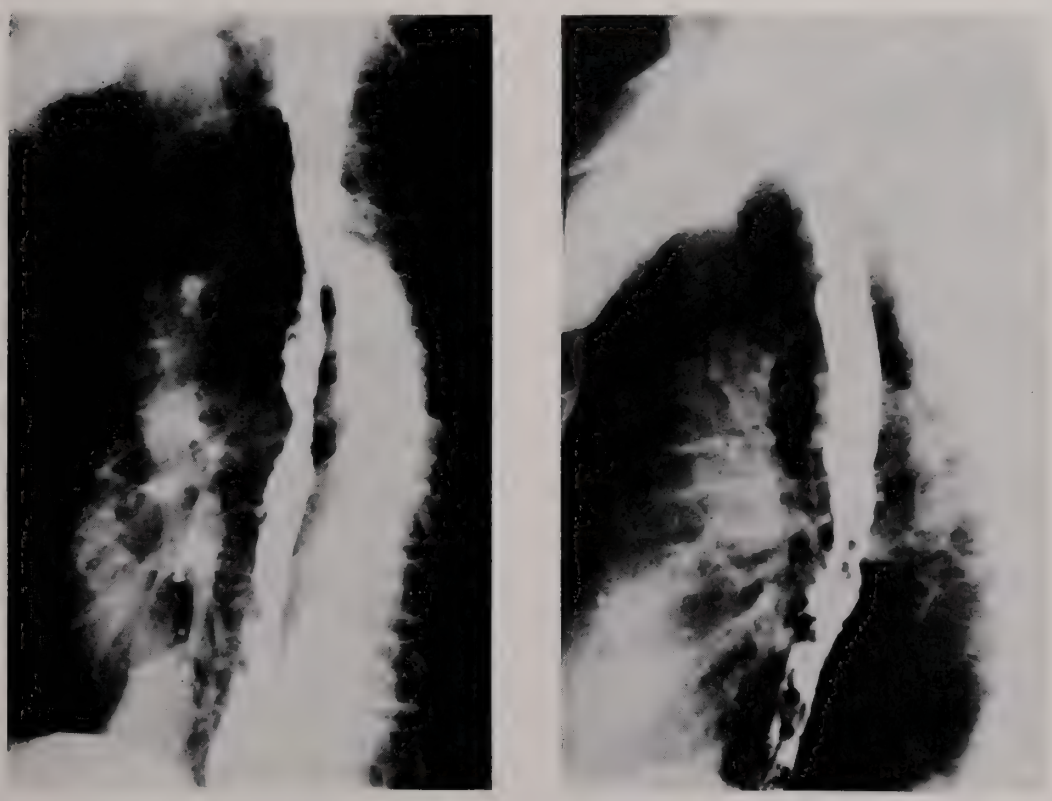
THIS 62-YEAR-OLD construction worker was referred to the University of Minnesota Hospitals with a chief complaint of pain on swallowing for several months. The pain was described as a burning, substernal sensation relieved by antacids and aggravated by swallowing both solids and liquids. The patient had lost weight. He had gone to his local physician one month prior to admission here after vomiting some bloody material. He gave no history of liver disease, although he admitted to "moderate" alcohol intake over many years.

General physical examination was unrewarding. Liver studies were normal.

Esophageal fluoroscopy revealed a very diffuse pattern of irregular, nodular filling defects extending from the cervical esophagus to the diaphragm (Figure) with little peristalsis apparent.

Esophagoscopy showed "large soft polypoid projections of mucosa" projecting into the lumen throughout the thoracic esophagus except for the very terminal portion. The mucosa over the "polyps" was intact, and their softness "did not suggest malignancy" to the examiners. Their impression was "diffuse polyposis of the esophagus." Multiple biopsies were taken.

What is your diagnosis? (See next page.)



Oblique Lateral

Figure

Diagnosis: Squamous Cell Carcinoma of the Esophagus.

Comment

The usual squamous cell carcinoma of the esophagus enlarges locally, frequently constricting and eventually obstructing the esophagus while still involving a relatively short segment. While it is well known that spread of the lesion mucosally or submucosally occurs very frequently beyond the site of the gross lesion, the extent of this spread is usually not apparent on esophagus films.

In a recent report, Minielly, Harrison, Fontana, and Payne describe an entity called "verrucous squamous cell carcinoma of the esophagus," a variety of carcinoma which tends to be exophytic in its growth pattern. While locally invasive, it tends to grow as a large mass within the esophagus and metastasizes rarely or late.[1] The tumor is thought to be similar to verrucous squamous cell carcinomas found much more commonly elsewhere (nasal and oral cavities, larynx, vagina).[2] Because of the different growth pattern, Minielly et al. felt early recognition and surgical treatment offered these patients a better chance for survival than the patient with the usual esophageal carcinoma. While the present case may or may not fit all the criteria for this morphological variant, it obviously spread mainly intrinsically as an exophytic, papillary growth, becoming very extensive before causing symptoms.

Differential diagnosis from the films might include esophageal varices,[3] and monilial esophagitis, which may produce gross irregularities in the barium swallow over the entire esophagus.[4] Leiomyomata, bulky adherent mediastinal lymph nodes, etc. may produce multiple defects in the barium column,[5] but should be more easily differentiated from the unusual squamous cell carcinoma presented here.

References

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3. Majcher, S. J.: Esophageal and Gastric Vascular Abnormalities Resembling Tumors. Gastroint Endosc 13:16, 1966.
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5. Glanville, J. N.: Leiomyomata of the Esophagus. Clin Radiol 16:187, 1965.

R. E. Anderson, M.D.*
Minneapolis, Minnesota

*Resident in Radiology, University of Minnesota Hospitals.

Dowieism

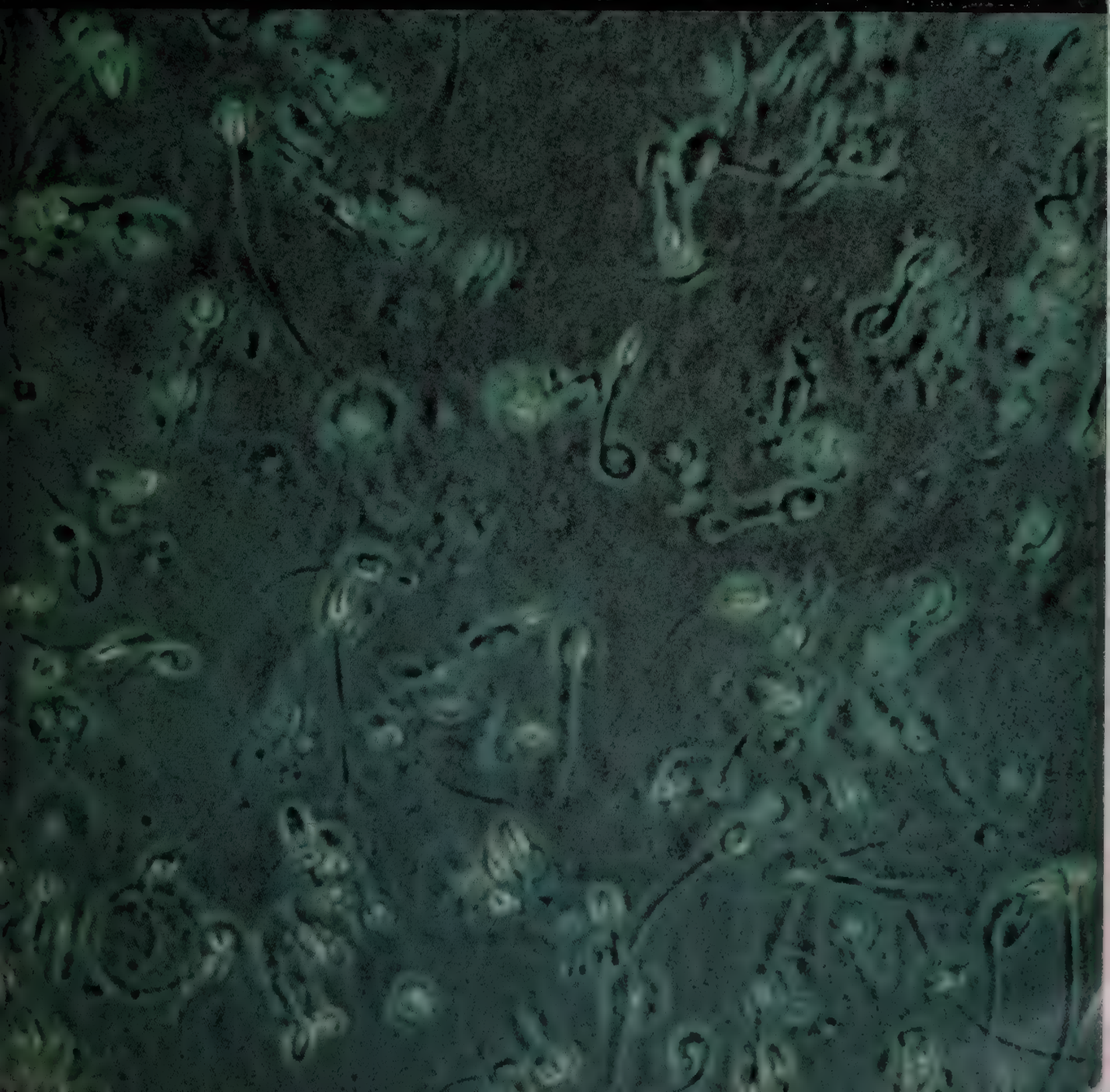
About 1900 Alexander Dowie announced that he was the prophet Elijah returned to earth, although without a chariot. He healed by the laying on of hands. His system was obviously faith healing. As a promoter Dowie was no doubt second only to Mrs. Eddy in this country. He built up a large following, established a city with tremendous industries and established church observances and ritual sufficient to occupy the minds of those who followed him. Like other prophets of healing he thundered against physicians and attacked preventive vaccination. When he passed on, the holy robes succeeded to Glenn Wilbur Voliva, now the czar of Zion City, the Jerusalem of the cult. Voliva thinks the world is flat.*

*Morris Fishbein, M.D.: The New Medical Follies, 1927.

When the talk turns to oral contraceptives, it makes medical sense to remember low-dose Norinyl®-1.

(norethindrone 1mg. & mestranol 0.05mg.)

Turn page for contraindications, precautions and side effects.



Reduction of oral contraceptive dosage to the lowest effective levels is a well-accepted principle of conservative medical practice. In keeping with this view, Norinyl is now also available as Norinyl-1, containing exactly one half the previous dosage of norethindrone and mestranol. Clinical experience has established that effective fertility control can be achieved with the same degree of reliability and safety with new Norinyl-1 when taken as directed.

What about switching patients from higher dosage forms?

In transferring patients to low-dose Norinyl-1 from higher-dosage oral contraceptives, some breakthrough bleeding may occur in the early cycles. In the majority of cases the bleeding episode is mild and self-limited. The long-term advantages of the lower dosage form should be weighed against the inconvenience of possible breakthrough bleeding in the individual patient.

Contraindications: 1. Patients with thrombophlebitis or with a history of thrombophlebitis or pulmonary embolism. 2. Liver dysfunction or disease. 3. Patients with known or suspected carcinoma of the breast or genital organs. 4. Undiagnosed vaginal bleeding.

Warnings: 1. Discontinue medication pending examination if there is sudden partial or complete loss of vision or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn. 2. Since the safety of NORINYL-1 (norethindrone 1 mg. with mestranol 0.05 mg.) in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. 3. Detectable amounts of the active ingredients in oral contraceptives have been identified in the milk of mothers receiving these drugs. The significance of this dose to the infant has not been determined.

Precautions: 1. The pretreatment physical examination should include special reference to breast and pelvic organs, as well as a Papanicolaou smear. 2. Endocrine and possibly liver function tests may be affected by treatment with NORINYL-1. Therefore, if such tests are abnormal in a patient taking NORINYL-1 it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, preexisting uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions that may be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. NORINYL-1 should be used with caution in patients with a history of cerebrovascular accident. 6. In relation to breakthrough bleeding, and as in all cases of irregular bleeding *per vaginam*, nonfunctional causes should be borne in mind. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated. 7. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 8. Any possible influence of prolonged NORINYL-1 therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. 9. A decrease in glucose tolerance has been observed in a small percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving NORINYL-1 therapy. 10. Because of the occasional occurrence of thrombophlebitis and pulmonary embolism in patients taking oral contraceptives, the physician should be alert to the earliest manifestations of the disease. 11. Because of the effects of estrogens on epiphyseal closure, NORINYL-1 should be used judiciously in young patients in whom bone growth is not complete. 12. The age of the patient constitutes no absolute limiting factor, although treatment with NORINYL-1 may mask the onset of the climacteric. 13. The pathologist should be advised of NORINYL-1 therapy when relevant specimens are submitted.

Side effects observed in patients receiving oral contraceptives: The following adverse reactions have been observed in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea, edema, chloasma or melasma, breast changes (tenderness, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately postpartum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals, mental depression.

Although the following side effects have been reported in users of oral contraceptives, no cause and effect relationship has been established: anovulation post-treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, itching.

The following occurrences have been observed in users of oral contraceptives (a cause and effect relationship has been neither established nor disproved): thrombophlebitis, pulmonary embolism, neuro-ocular lesions.

The following laboratory results may be altered by the use of oral contraceptives: increased sulfobromophthalein and other hepatic function tests, coagulation tests (increase in prothrombin, Factors VII, VIII, IX and X), thyroid function (increase in PBI and butanol extractable protein-bound iodine and decrease in T^3 values), metyrapone test, pregnanediol determination.

norethindrone — an original steroid from

SYNTEX

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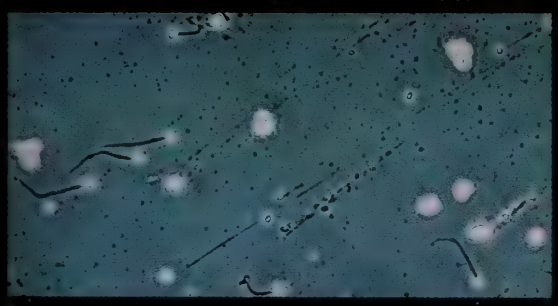
Here's why Norinyl-1 makes medical sense.

The effectiveness of Norinyl-1 as a low-dose oral contraceptive may be explained by its possible multiple action. In addition to its primary action of suppression of ovulation, Norinyl-1 may offer additional protective mechanisms... (1) creation of a cervical mucus that may be hostile to sperm penetration, and (2) development of an endometrium that may be out of phase with nidation. These effects are illustrated below.

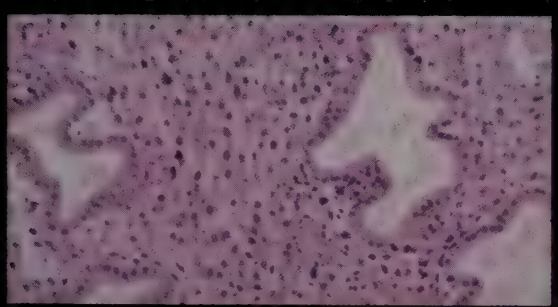
Untreated Patient



Cervical mucus at midcycle is usually thin and watery, with Spinnbarkeit (stretchability) of 15 to 20 cm.

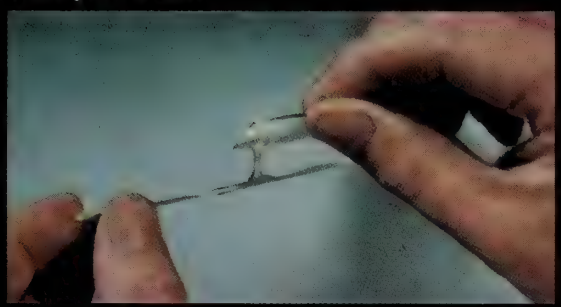


Spermatozoa appear healthy, active, freemoving.

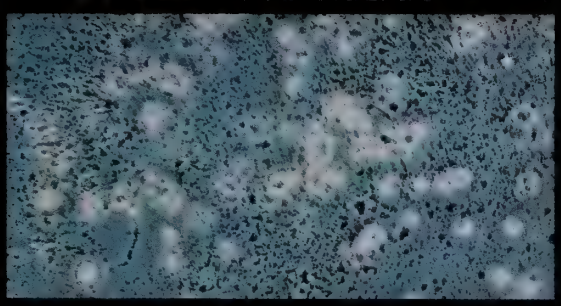


Endometrium of untreated patient is receptive to the fertilized ovum during secretory phase.

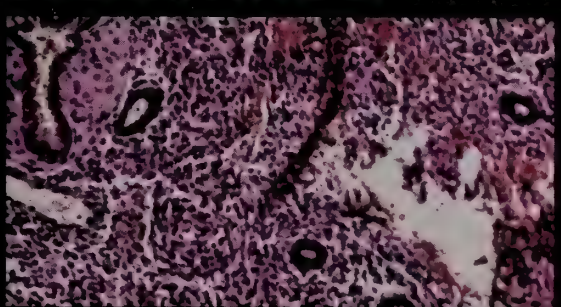
Norinyl-1 Patient



Cervical mucus at midcycle is scanty, viscous—with Spinnbarkeit of 1 cm. or less.



Immobile spermatozoa as they appear in cervical mucus taken from patient treated with Norinyl-1.



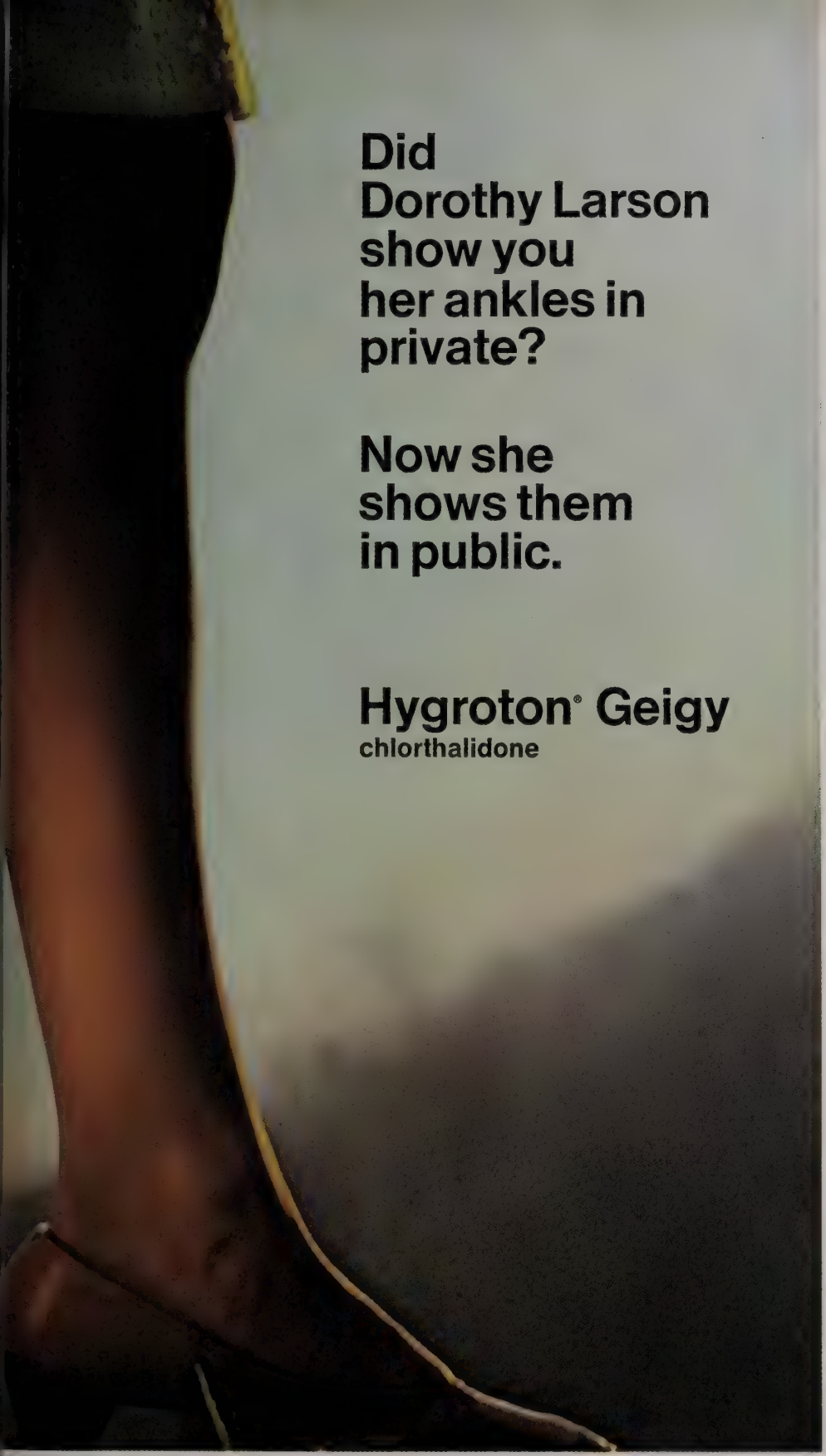
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Indications: Hypertension and many types of edema involving retention of salt and water.
Contraindications: Hypersensitivity and most cases of severe renal or hepatic disease.
Warning: With the administration of enteric-coated potassium supplements, which should be used only when adequate dietary supplementation is not practical, the possibility of small bowel lesions (obstruction, hemorrhage, and perforation) should be kept in mind. Surgery for these lesions has frequently been required and deaths have occurred. Discontinue enteric-coated potassium supplements immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur. Use with caution in pregnant patients, since the drug may cross the placental barrier and adverse reactions which may occur in the adult (thrombocytopenia, hyperbilirubinemia, altered carbohydrate metabolism, etc.) are potential problems in the newborn.
Precautions: Antihypertensive therapy with Hygroton should always be initiated cautiously in postsympathectomy patients and in patients receiving ganglionic blocking agents or other potent antihypertensive drugs, or curare. Reduce dosage of concomitant antihypertensive agents by at least one-half. Barbiturates, narcotics or alcohol may potentiate hypotension. Because of the possibility of progression of renal damage, periodic determination of the BUN is indicated. Discontinue if the BUN rise or liver dysfunction is aggravated. Hepatic coma may be precipitated Electrolyte imbalance, sodium and or potassium depletion may occur If potassium depletion should occur during therapy, Hygroton shou be discontinued and potassium supplements given, provided the



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Hygroton therapy may mean troublesome side effects for some patients. A summary of the prescribing information is shown below.

patient does not have marked oliguria.
Take special care in cirrhosis or severe ischemic heart disease and in patients receiving corticosteroids, ACTH, or digitalis. Salt restriction is not recommended.
Adverse Reactions: Nausea, gastric irritation, vomiting, anorexia, constipation and cramping, dizziness, weakness, restlessness, hyperglycemia, hyperuricemia, headache, muscle cramps, orthostatic hypotension, aplastic anemia, leukopenia, thrombocytopenia, agranulocytosis, impotence, dysuria, transient myopia, skin rashes, urticaria, purpura, necrotizing angiitis, acute gout, and pancreatitis when epigastric pain or unexplained G.I. symptoms develop after prolonged administration. Other reactions reported with this class of compounds include: jaundice, xanthopsia, paresthesia, and photosensitization.
Average Dosage: 50 or 100 mg. with breakfast daily or 100 mg. every other day.
Availability: White, single-scored tablets of 100 mg. and aqua tablets of 50 mg., in bottles of 100 and 1000.
(B)R46-230-D
For full details, please see the complete prescribing information.

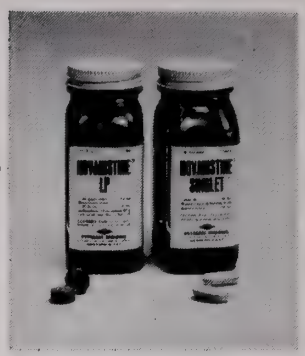
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Each Novahistine LP tablet contains phenylephrine hydrochloride, 25 mg.; and chlorpheniramine maleate, 4 mg.
Each Novahistine Singlet tablet contains phenylephrine hydrochloride, 40 mg.; chlorpheniramine maleate, 8 mg.; and acetaminophen, 500 mg.

With Novahistine LP tablets and Novahistine Singlet™ tablets you have the range and flexibility of decongestant dosage that lets you prescribe for the needs of the individual patient.

Novahistine LP tablets are most useful for relief of nasal congestion in patients without pain or fever. Novahistine Singlet tablets, which provide analgesic-antipyretic effect, as well as decongestant action, are indicated for upper respiratory infections accompanied by pain, aches and fever.

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Tumor Conference

Insulin-Secreting Tumors of the Pancreas

LOCALIZATION OF lesions in the pancreas is a much needed advance in preoperative evaluation of pancreatic tumors, particularly for small tumors such as insulinomas which are often difficult to locate at surgery. Recently, there has been increasing use of selective arteriograms for demonstrating lesions in many areas of the body. The following case report describes the use of pancreatic arteriography in the preoperative localization of a 1.5-cm. insulinoma.

Case Report

A 25-year-old white male was admitted to the Veterans Administration Hospital with a three-month history of episodes of weakness, disorientation and bizarre behavior, which usually occurred in the morning. He recalled these episodes poorly, but did remember that he sought candy for relief. He gave no history of sweating, tachycardia or nervousness. On the day of admission to the emergency room of another hospital, the patient had become unconscious. A blood sugar drawn at this time was reported to be 23 mgm %. On admission to our hospital, the patient appeared healthy but was less alert than normal with a somewhat obtunded sensorium. Physical examination was normal.

Laboratory studies were also normal with the exception of the glucose tolerance test. The following values were obtained: fasting value 52 mgm%; 30 min., 116 mgm%; 1 hr., 123 mgm%; 2 hrs., 132 mgm%; 3 hrs., 120 mgm%; 4 hrs., 60 mgm%; 5 hrs., 50 mgm%; 6 hrs., 30 mgm%.

Selective superior mesenteric and celiac arteriograms were performed. An increased area of vascularity was noted in the mid portion of the gland (Figure 1). During the preoperative evaluation, the patient had frequent administration of oral glucose except when special studies were performed. He experienced no more hypoglycemic episodes and demonstrated normal behavior.

The patient had an exploratory laparotomy six days after admission. Located in the proximal portion of the tail of the pancreas was a 1.5-cm. nodule which presented on the surface as a wine-colored nodule of approximately 0.5 cm. The true size of the lesion was appreciated as it was shelled out. On cut section, the tumor was pale yellow. The remainder of the gland was carefully inspected and palpated, and no further nodules were found.

Following surgery, the patient made a satisfactory recovery. Repeated blood sugars were all in the normal range. He has returned to work and has had no return of symptoms.

Discussion

Several aspects of this case are worthy of note. It is a relatively rare tumor. The largest series is that collected by Howard, et al.,[3] which consists of a survey of the literature and includes 361 localized tumors, 200 of which were operated for hyperinsulinism, and 161 discovered at autopsy. In

this and other series, the generally reported incidence of multiple adenomas is approximately 10%. Ten percent may also be carcinomatous.

The diagnosis of insulinoma can most surely be made in a patient demonstrating Whipple's triad: (1) symptoms of insulin shock frequently induced by the fasting state or during exercise, (2) repeated fasting blood sugar levels below 50 mgm%, (3) relief of symptoms by administration of glucose. Attacks may occur daily or once or twice a year for several years. Other helpful tests include a fasting tolerance test, which usually lasts for 12 to 36 hours. During this time, any symptoms of insulin shock are watched for and a blood sugar drawn. Exercise during this fasting period may provoke a typical hypoglycemic attack in a shorter period of time. In any case, the *sine qua non* is a return of symptoms with a documented glucose level of less than 50 mgm%.

Once surgery has been decided upon, preoperative knowledge of the exact location of the tumor is extremely helpful, since the tumors are distributed equally in the head, body, and tail. Careful mobilization and palpation of the entire gland will usually disclose the location of the tumor nodule. The majority are encapsulated and measure between 1.0 and 3.0 cm. They can

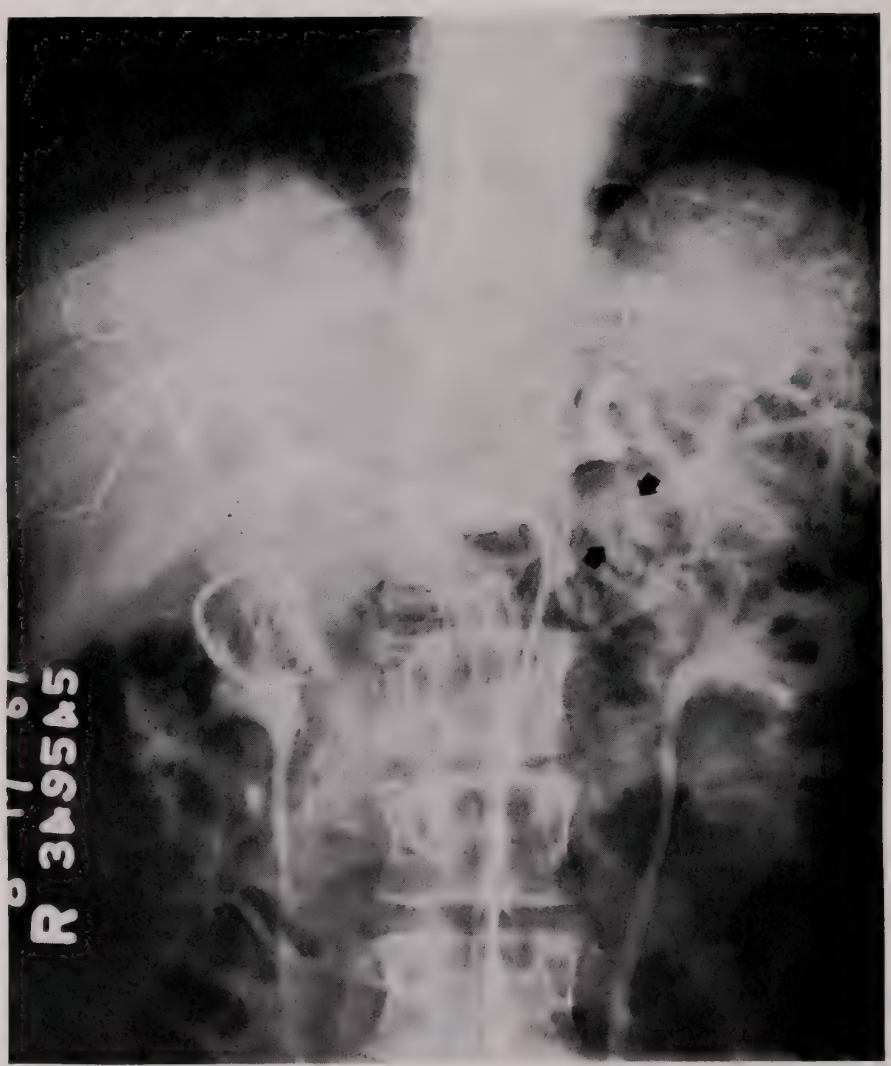


Fig. 1—Pancreatic arteriogram—catheters are visible in the celiac and superior mesenteric arteries. Increased tumor stain is seen between arrows.

be shelled out, although location or size may require resection of the pancreas. If no tumor is found, some recommend a "blind" distal pancreatectomy.[1,2] Howard et al.[3] found this to give a satisfactory therapeutic result in 46% of 56 patients. Recently, Miller[4] and Fonkalsrud et al.[5] have questioned the advisability of such an approach and, in fact, suggest that an occult tumor may more likely be in the head of the gland rather than in the tail.

Preoperative selective pancreatic angiography has been recommended to obviate some of these problems at the time of surgery. The use of angiography for the diagnosis of insulinomas was first reported by Olsson in 1963.[6] Dye injected simultaneously into the hepatic and superior mesenteric arteries demonstrated an islet-cell adenoma 1.5 cm. in diameter in the head of the pancreas. Baun et al.[7] identified four islet-cell tumors by angiography. The success of this study, however, depends on the vascularity of the tumor, i.e., whether the dye will stain the area. In six cases of insulinoma reported by Brookstein and Oberman,[8] the tumor was visualized by arteriogram in only two. Histologically these tumors show wide variability with regard to vascularity and will stain best if comprised of dilated blood-filled sinusoids. In reviewing other slides, this type of histological picture was found some-

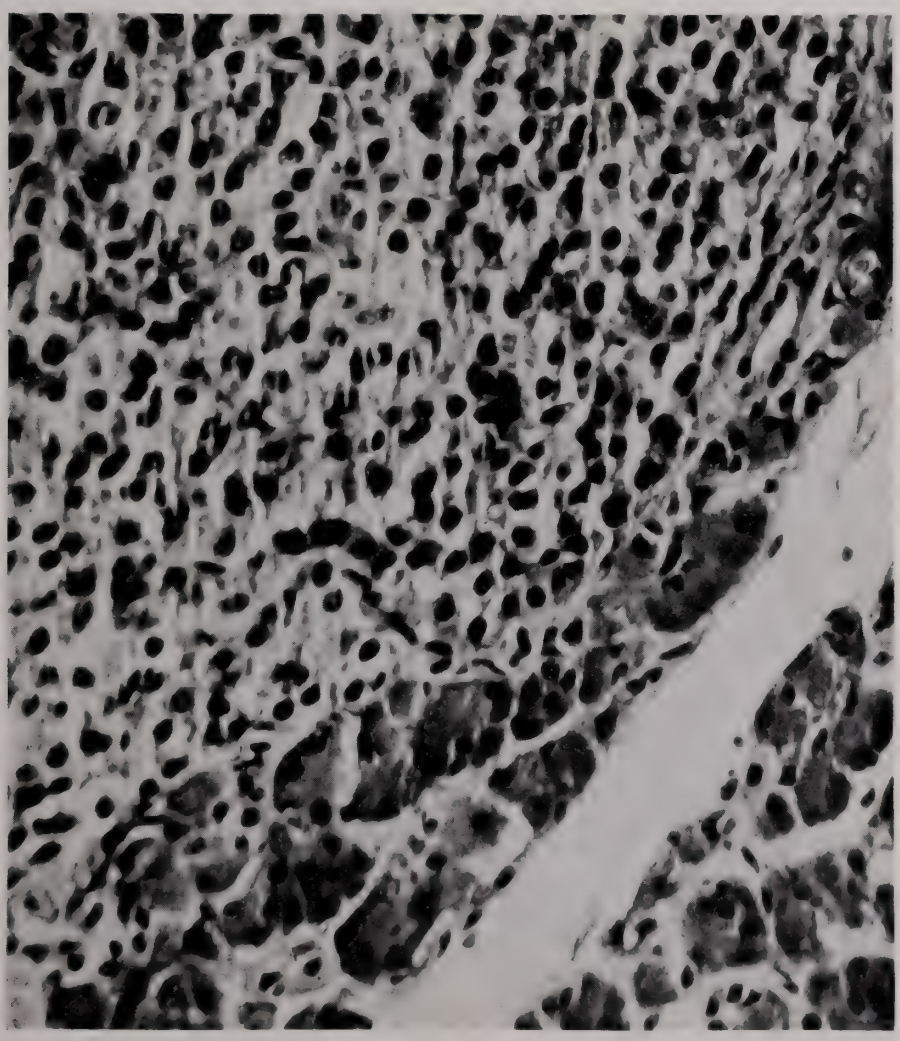


Fig. 2—Histology of tumor—Note homogeneous appearance without marked vascularity. A small amount of normal pancreatic tissue is visible. (Hematoxylin and eosin stain x 200).

what less than 20% of the time. The authors predict, therefore, that in only 20% of insulinomas will a tumor stain be identified. Nevertheless, the test seems to be a reasonable one because of the low morbidity and possible substantial advantage gained by knowledge of the location of the tumor.

X-ray studies in this case accurately suggested the possible location of the lesion as being in the mid portion of the gland. Fortunately it was on the surface and visible, but knowing in which area to concentrate was helpful. The histology of the specimen showed nests of islet cells without marked vascularity (Figure 2). A more positive tumor stain in this case would not have been possible.

Summary

The advantage of preoperative pancreatic arteriography in localization of an insulin-secreting tumor is demonstrated in this case report.

Episodes of tremulousness, disorientation and a low blood sugar at the time of maximum symptoms should lend suspicion to the diagnosis of insulinoma.

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Saints and Medicine

Familiar as an April saint is Bernadette (1844-1879), identified with the shrine at Lourdes, France, the healing powers of whose grotto waters were revealed to her as a young girl by the Virgin Mary. This shrine became world-famous and continues to this day to be a Mecca for the ailing who believe in the curative properties of its waters and are sometimes mysteriously and inexplicably benefited thereby.

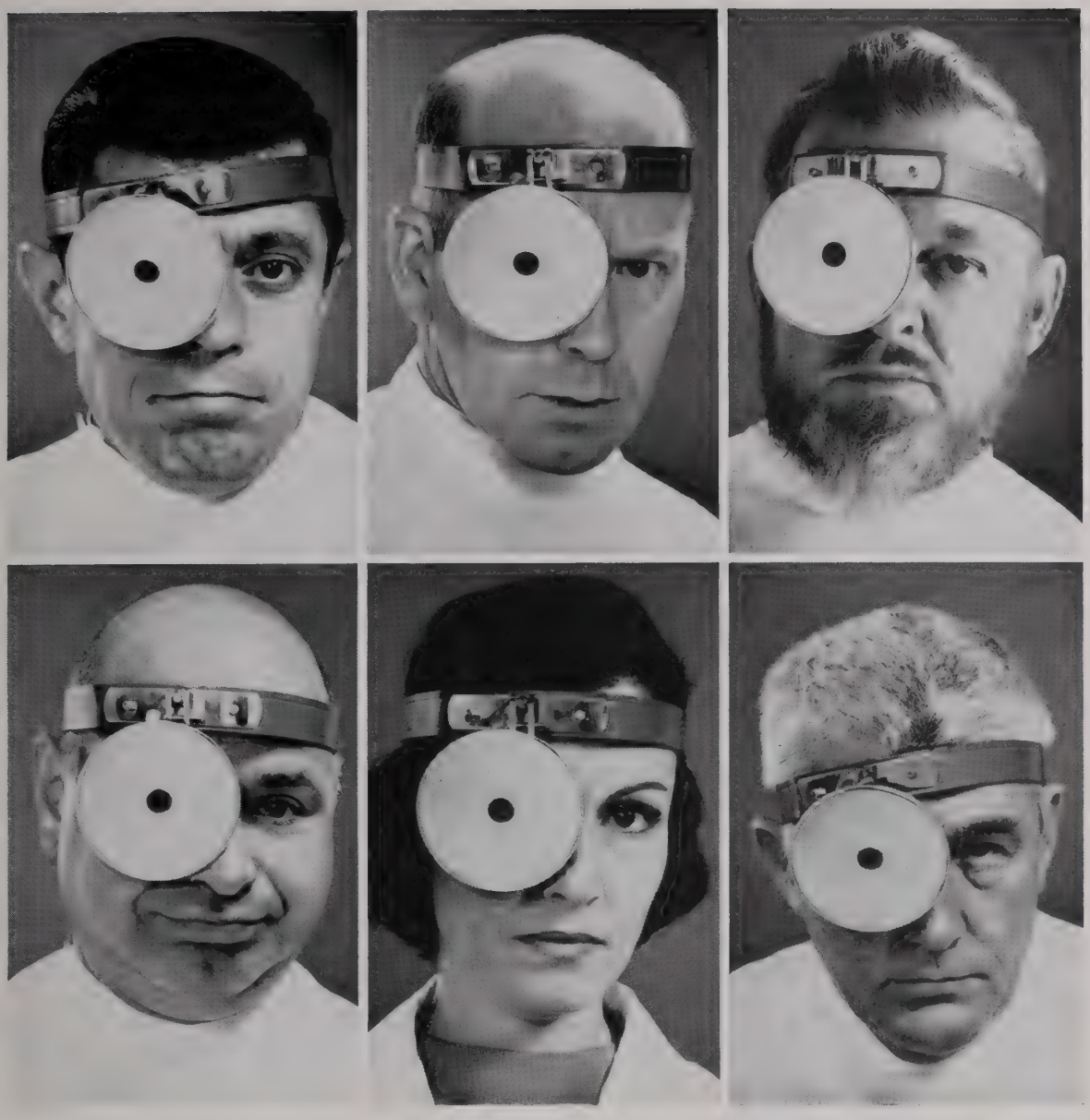
St. Bernadette's commemorative day is April 16.

Losses

A man loses his illusions first, his teeth second, and his follies last.—Helen Rowland

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Dermatology

Argyria

In a recent article, contact sensitivity to nickel was discussed. Another interesting clinical problem with respect to metals is their deposition within the skin. This may produce either generalized or local discolorations. Metals may reach the skin either by local absorption or by way of the blood stream. As a rule, the latter route results in the general color changes associated with such metals as silver.

Argyria—This condition which results from either ingestion or the local application of silver salts and colloidal silver is characterized by a slate-blue cutaneous pigmentation. Silver nitrate, argyrol, protargol and silver arsphenamine have all been responsible, although the former use of silver nitrate internally probably accounted for the greatest number of cases. Today one may occasionally see new cases in chemical workers and workers in related occupations where silver nitrate is employed.

Argyria may be either localized or generalized. If topical application of silver nitrate has been used for a prolonged period (such as on an ulcer), the



Figure

local form of this condition may result. When argyrol was more frequently used as eyedrops, at times a diffuse periocular pigmentation resulted from absorption and diffusion of the drug. However, when silver in its several forms has been applied to mucous membranes where absorption is good or administered internally, the generalized type of pigmentation can ensue. At first the discoloration is barely perceptible and only gradually deepens, with the most pronounced changes occurring on the light-exposed areas, such as the face, conjunctiva, hands, and under the fingernails. Although the condition is clinically evident on the skin, involvement of the internal organs also occurs.

Argyria can be diagnosed very easily from a skin biopsy. Under darkfield illumination granules of silver may be seen in the lamina propria of the sweat glands (Figure), in the connective tissue sheaths of hair follicles and sebaceous glands, in the walls of blood vessels and in nerve bundles. In addition, the silver granules may be scattered diffusely throughout the dermis. Although darkfield illumination nicely demonstrates the silver, hematoxylin and eosin-stained sections also reveal granules of silver on close inspection. Of interest in this condition is the fact that the clinical coloration is not due to silver but rather to increased deposition of melanin. It appears that silver along with certain other metals has the property of stimulating melanocytic activity. Although silver is found in equal amounts in both exposed and non-exposed areas, melanin is increased far more in the light-exposed areas. For this reason the bluish pigmentation is greatest on these areas. This melanin is found both in the epidermis and below in the dermis. It is this melanin in the deeper layers of the dermis which gives the patient the slate-blue coloration. The reason for this phenomenon is stated to be that of light scattering (Tyndall effect), with blue light scattered to a greater extent than red light when passing through a turbid medium. Therefore, when pigment such as melanin lies in the dermis rather than the basal layer of the epidermis, it appears bluish.

Other—Several other heavy metals may cause slate-colored pigmentation. Gold, when given parenterally, may lead to this development, which is also most marked on areas exposed to ultraviolet light. This condition is referred to as *chrysiasis*. Bismuth, when given internally, may be associated with diffuse pigmentation or a localized variant (bismuth line on the gums). Both bismuth and mercury have in the past been used in certain cosmetic preparations (freckle creams) which lead to localized discolorations on the face and neck. With none of these conditions is it possible to reverse the pigmentary changes once they have occurred. However, eliminating the use of heavy metals and reduction of sun exposure may reduce the degree of pigmentation resulting from their use.

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Minneapolis, Minnesota

*Division of Dermatology, Department of Medicine, University of Minnesota Hospitals, Minneapolis.

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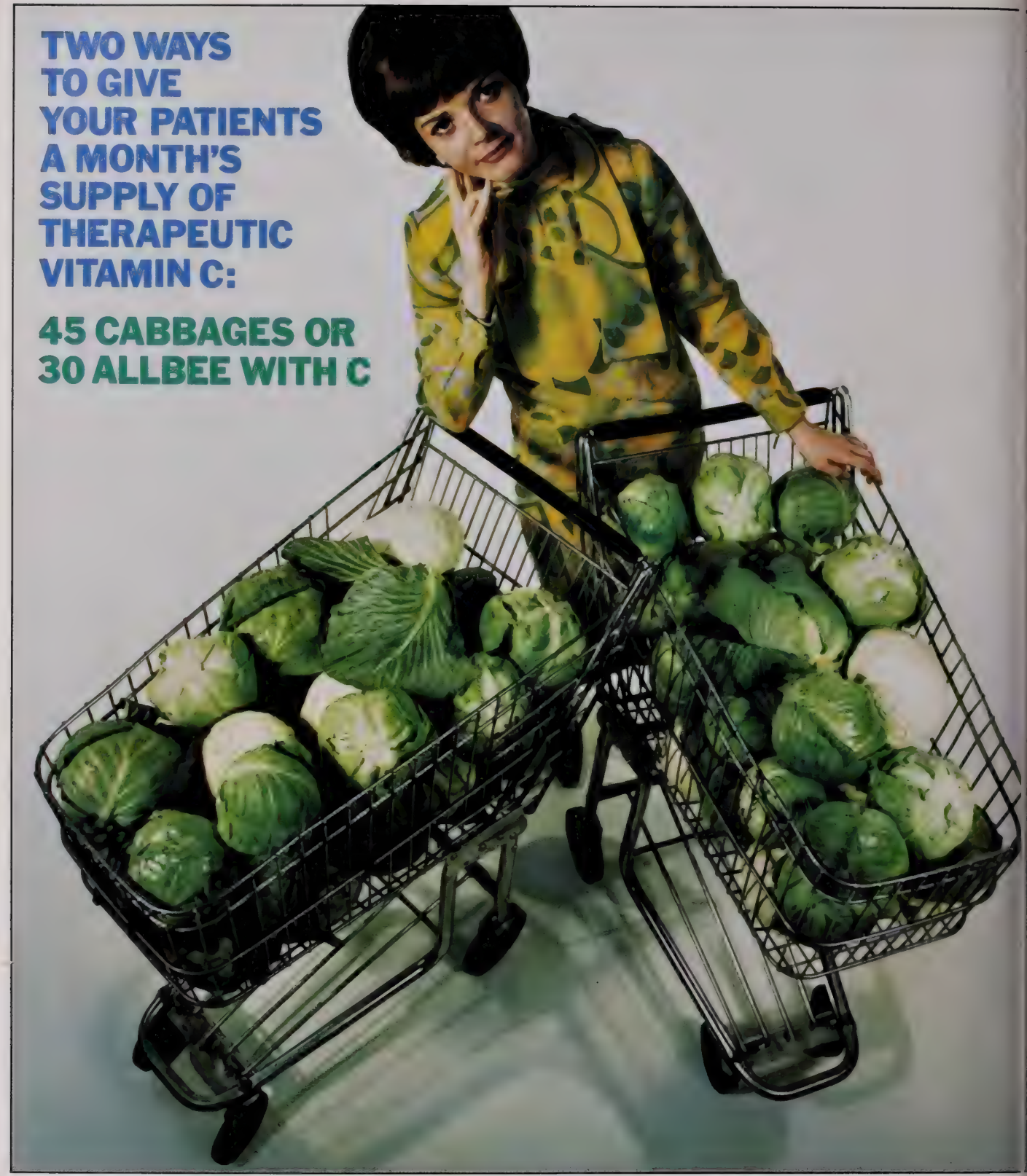
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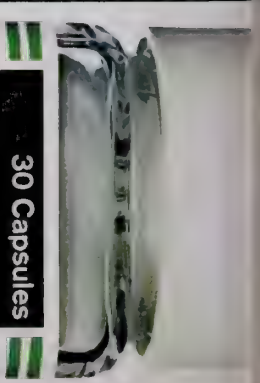


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Grand Rounds

Biochemical Factors Related to the Serum Cholesterol Levels*

ARNOLD W. LINDALL, M.D., Ph.D.
Medical Resident

THE FREQUENT occurrence of elevated serum cholesterol levels in the presence of vascular disease is a generally known phenomenon. Analysis of fatty plaques in the intima of the human thoracic aorta reveals a 500% increase of cholesterol compared to normal intima; while in contrast other lipids are either normal or only slightly elevated.[1] It is not surprising, therefore, that much research effort has been devoted to the clinical and biochemical facets of cholesterol metabolism in the hope that effective means to lower serum cholesterol can be found. The control of malignant accumulations of lipid would be easier if the dynamic interrelationship between the tissue and serum pools were well understood. In reality, this can come only with basic research at the cellular level. The dangers of using poorly understood drugs to lower serum cholesterol were underscored recently with the introduction of triparonal, which had dangerous side effects related to the accumulation of a sterol intermediate, desmosterol.[2] Our purpose here will be to lay a basic foundation of knowledge about the biology of cholesterol and its relation to the clinical problem of hypercholesterolemia. The following topics will be discussed.

- Cholesterol absorption and clearance
- Plasma cholesterol configuration
- The classification of hyperlipoproteinemias
- Elements in the control of cholesterol synthesis in liver and intestine
- Evidence related to the site of action of chlorphenoxyisobutyrate
- Future research

*Presented as a Medical Grand Rounds at Hennepin County General Hospital, November 7, 1967.

Cholesterol Absorption and Clearance

Goodman[3] recently reviewed the massive body of information on cholesterol esters. From his extensive documentation the following scheme related to dietary cholesterol absorption and disposal can be drawn. Cholesterol in the diet is absorbed in the small intestine in the presence of bile and pancreatic enzymes. Bile is necessary for solubilization, and the enzymes are necessary for cleavage of the fatty acid moiety of cholesterol esters. Only free cholesterol is transported into gut endothelium in a mechanism not related to pinocytosis. Dietary cholesterol is mixed in the intestine with cholesterol secreted in the bile. There is an enterohepatic circulation of one to three grams per day of the circulating cholesterol. In contrast to plasma, the biliary cholesterol is mainly in the free state, probably because of the presence of the surface active materials in bile. The biliary constituents themselves have interesting effects on endogenous intestinal cholesterol synthesis, as will be discussed later. Bile salt formation, of course, is one of the pathways of cholesterol metabolism.

While only free cholesterol is absorbed, it is soon esterified again and appears in the intestinal lymph in the chylomicron fraction in association with triglycerides. Evidently the intestinal microsome fraction is responsible for esterification. Peak absorption of cholesterol in man is at about nine hours post prandial.

Lymph chylomicrons are cleared by the liver parenchymal cells by pinocytosis. The heparin-activated clearing factors may be related to this process. Esterases present in both microsomal and soluble fractions are capable of freeing cholesterol from the ester form. In turn, free cholesterol can be esterified in a reaction involving microsomes, adenosine triphosphate, fatty acids, coenzyme A and cholesterol. Cholesterol oleate is the favored product. Conjugated bile salts and long-chain fatty acids inhibit this reaction in vitro.[4] The latter observations are of importance in the use of cholestyramine to lower serum cholesterol and also in the understanding of the increased free cholesterol observed in obstructive liver disease.

Dietary cholesterol is diluted with endogenously synthesized cholesterol in the liver; however, liver cholesterol ester content tends to reflect the dietary cholesterol ester pattern with regard to the fatty acid moiety. The liver, of course, is involved in plasma lipoprotein synthesis, bile salt formation and the synthesis of its own membrane systems; each of these processes consumes cholesterol and therefore affects plasma cholesterol levels.

Plasma Cholesterol Configuration

Plasma cholesterol is associated with the lipoprotein fractions and is over 80 percent esterified in contrast to tissue cholesterol which is almost all free except in the adrenal gland. It is convenient to view the lipoproteins as part of the structure of a liquid tissue, the blood, and as principally related to triglyceride transport. The presence of cholesterol may well not be related to cholesterol movement from liver to tissue; but rather cholesterol may be a structural component of the lipoproteins, just as it is in all membranes. Elevated cholesterol levels in serum should be considered in the broader context as lipoprotein abnormalities and disease classified on this basis. In order to understand current classifications of lipoproteins some understanding of methodology is necessary.

Ultra Centrifugation of Serum

Lipoproteins are separated from other serum proteins most readily by the preparative ultracentrifuge. In this instrument serum is exposed to gravitational forces of 10,000-200,000 x gravity. Such forces will ordinarily cause proteins to migrate to the bottom of a centrifuge tube. The rate of migration is a function of molecular weight, shape, and density of the protein; the other factors are the density of the media and the force applied. The quantitative description[5] known as the Svedberg equation is:

$$v = \frac{dx}{dt} = \frac{\emptyset\ (\rho_p - \rho_m)}{F} \quad w^2x$$

v = radial velocity
$\emptyset$ = particle volume
ρ_p = particle density
ρ_m = media density
F = frictional coefficient
w = rotational velocity
x = distance from rotor center

In a liquid medium particles reach a terminal velocity rapidly and then migrate at a rate directly proportional to centrifugal acceleration such that the velocity of the particle divided by the rotational force is a constant. This constant is known as the sedimentation coefficient and is a means of describing a protein in solution. The quantitative description is:

$$s = \frac{v}{w^2x} = \frac{\emptyset(\rho_p - \rho_m)}{F}$$

Usually this value is standardized to the density of water at 20°C. S $\times$ 10^{13} is equal to one Svedberg, which is the unit of description.

It can be seen that S can be postive or negative depending on the medium density. If the protein molecule is less dense than the medium, the protein molecule migrates toward the center of the rotor and S is negative. The standard condition to describe negative S is a density of 1.063. Particles which float in such a medium are classified by their flotation constant (S_F), which is the negative of the S constant. Lipoproteins which float under these conditions have S_F values from 0 to greater than 400. Various lipoproteins

TABLE 1
Clinically Important Classes of Lipoproteins Compiled from Fredrickson et al.[6]

Density of Media	G Forces	Protein Fraction Floated	S F	Class	Comments
1.006	10,000 xg 10 min.	Chylomicrons	400	very low density lipoproteins	exogenous glyceride particles
1.006	100,000 xg 24 hrs.	Pre beta lipoprotein	20-400	very low density lipoproteins	endogenous glyceride particles
1.063	100,000 xg 24 hrs.	Beta lipoprotein	0-20	low density lipoprotein	contains small amt. alpha lipoprotein known as HDL-1
1.021	100,000 xg 24 hrs.	Alpha lipoprotein	...	high density lipoprotein	subfractions called HDL-2 and HDL-3

are classified into high density, low density and very low density, based on their S_F or S values.

In practice, separate species of lipoproteins can be collected by incrementally increasing the density of serum with additions of sodium chloride and potassium bromide and carrying out successive centrifugations.[7] The first two centrifugations are done at the natural density of protein-free serum (1.006). The increments of density for the next centrifugations are 1.063 which floats the beta lipoproteins away from alpha lipoproteins* and 1.021 which floats the alpha lipoproteins from the other serum proteins. The nomenclature for the various fractions is collected in Table 1.[6]

The Soluble Lipoproteins[6]

The terms, alpha and beta lipoproteins refer to the migration of these lipoproteins on ordinary paper electrophoresis. Alpha lipoproteins migrate with alpha globulins and beta lipoproteins with beta globulins. With fat-soluble stains such as sudan black and oil red-o, the lipid component of such proteins can be easily stained. In any lipoprotein there can be up to four components.

1. A specific apoprotein.
   Proteins designated as A, B and possibly C have been recognized. The A protein is related to alpha lipoproteins while B is related to beta lipoproteins.
2. Phospholipids.
3. Cholesterol chiefly as esters.
   The smaller percentage of free cholesterol may be extremely important in exchange reactions and actual cholesterol transport.
4. Triglycerides.

Alpha lipoproteins contain 45-55% protein, 30% phospholipid, 18% cholesterol, and very little triglyceride. In contrast beta lipoproteins contain 20-25% protein, 22% phospholipid, 43% cholesterol and 10% triglyceride. In terms of content the beta lipoproteins are the major contributors to the serum cholesterol. From a study[7] which I use only as a sample, the cholesterol contents of the soluble lipoproteins are shown (Table 2).

TABLE 2
Cholesterol Content of Lipoproteins in 10 Fasted Normal Males after Havel et al.[7] units mg.% original serum ± SD

Density Class	Type	Cholesterol	Phospholipid	Cholesterol Phospholipid
1.019	Very low density + small amount of beta	26 ± 8	31 ± 9	0.84 ± 0.09
1.019-1.063	beta	97 ± 22	69 ± 13	1.41 ± 0.13
1.063	alpha	43 ± 5	111 ± 1	0.38 ± .06

In this sample 62% of the cholesterol was in the beta lipoprotein while only 28% was in the alpha fraction. The alpha cholesterol was more heavily esterified.

*A small amount of alpha lipoprotein known as HDL-1 comes with the beta fraction.

The Very Low Density Lipoproteins[8]

The fractions which carry the major load of triglyceride are the chylomicrons and so-called pre-beta lipoproteins.[1] Chylomicrons are the large particles from 0.1-5.0 microns in diameter which occur normally after a fatty meal, thus accounting for the name, exogenous glyceride particles. They consist of two components separable by starch-block electrophoresis; however, with paper electrophoresis they remain at the origin, thus being separable from pre-beta particles. Pre-beta lipoproteins occur after high carbohydrate diet or in normal fasted individuals. They are more dense and smaller than chylomicrons, and since they originate in the liver they are called endogenous glyceride, signifying the possible origin of the glyceride from hepatic synthesis. The protein content of these particles is very low, being 2.5% for chylomicrons and 2-15% for the pre-beta fraction. The lipid content for chylomicrons is 2-12% cholesterol, 3-15% phospholipid and 79-95% triglyceride. For the pre-beta class of protein, the lipid content is 10-25% cholesterol, 15-25% phospholipid and 50-80% triglyceride. The ratio of cholesterol to phospholipid and the type of protein is consistent with the presence of alpha and beta lipoprotein coated or containing triglyceride for transport.

The Classification of Hyperlipoproteinemias[9,10,11]

Five groups of abnormal lipoprotein patterns based on electrophoresis, centrifugation and genetic factors have been described.

Type I

Increased chylomicrons 14 hours after last meal. Alpha and beta lipoproteins may be decreased and free cholesterol levels may approach 50% of total. In the inherited form the heparin-activated lipoprotein lipolytic activity in serum is decreased. The best treatment appears to be dietary fat restriction; however, this may only change the serum lipids to pre-beta types. *The plasma is milky.* Other changes are increased size of the liver and spleen, lipemia retinalis and yellow skin papules. The glucose tolerance is normal.

Type II

Increased true beta lipoproteins with triglycerides not generally greater than 150 mg. %. *The plasma is clear.* A small increase in the pre-beta fraction is possible. The occurrence is frequently familial and is the most common inherited hyperlipidemic disease. The secondary pattern occurs in hypothyroidism, nephrotic syndrome and occasionally in liver disease. Tendon xanthomas are common as well as arcus senilis. Carbohydrate intolerance is not necessarily present and atherosclerosis is common. Treatment with low cholesterol-high unsaturated fat diets is successful in some cases. Drug treatment is not well established.

Type III

Increased beta lipoproteins that have a density less than 1.006 with an increase in pre-beta proteins as well. This pattern must be established with the ultracentrifuge. *The plasma is turbid* and the beta electrophoresis band is very broad. A curious diagnostic feature is lipid deposition in the palms. There is also xanthomatosis. Clinically there are increased serum cholesterol and triglycerides and often abnormal glucose tolerance. There is a familial form; the basic defect may be in the breakdown of the pre-beta proteins. Treatment includes weight reduction, unsaturated fats and low dietary cholesterol. Drugs such as Atromid may be useful.

Type IV

Increased pre-beta lipoproteins *with turbid plasma.* Triglycerides are increased and a modest cholesterol increase may occur. Alpha and beta lipoproteins are decreased. Carbohydrate diets induce this pattern in those individuals affected. Xanthomatosis, obesity, abnormal glucose tolerance and atherosclerosis are common. Familial occurrence is not well resolved. A secondary type may be present in insulin-sensitive ketotic diabetics and in pancreatitis. Insulin is less effective in the primary type IV defect. Other common diseases are glycogen storage disease, hypothyroidism, nephrotic syndrome, idiopathic hypercalcemia and alcoholism. Treatment may be by weight reduction and avoidance of high-carbohydrate diets. Atromid may be useful.

Type V

Increased chylomicrons and pre-beta lipoproteins after a normal diet with *a turbid or milky plasma.* This may not be a pure disease and a familial relationship is unclear. It may also be secondary to diabetes, alcoholism or pancreatitis. Treatment is by weight reduction. Neither dietary fats nor carbohydrates should be emphasized. Drug effects are not known.

Obstructive liver disease is considered separately by Fredrickson et al.[11] since the lipidemia is largely free cholesterol and phospholipid. High density lipoproteins are diminished.

For practical purposes the range of lipids in the various lipoproteins in fasted normals is presented in Table 3 from the data of Fredrickson et al.[9]

TABLE 3
Range of Normal Lipids by Protein Class[9]
Units: mg.%

Age Range	No. of People	Total Cholesterol	Triglyceride	Pre-beta Cholesterol	Beta Cholesterol	Alpha Cholesterol Males	Alpha Cholesterol Females
0-19	81	120-230	10-140	5-25	50-170	30-65	30-70
20-29	78	120-240	10-140	5-25	60-170	35-70	35-75
30-39	82	140-270	10-150	5-25	70-190	30-65	35-80
40-49	111	150-310	10-160	5-25	80-190	30-65	40-85
50-59	69	160-330	10-190	10-40	80-210	30-65	35-85

Elements in the Control of Cholesterol Synthesis in Liver and Intestine

Cholesterol is apparently synthesized by all tissues; however, the chief source of endogenously synthesized plasma cholesterol is probably the liver. In reality what is formed is a lipoprotein complex; but the mechanism of this formation is unknown. There is also a contribution to plasma cholesterol from the intestine.

Liver

Only a very general scheme of the biochemical steps of cholesterol synthesis will be reviewed. The history and elucidation of these reactions was reviewed by Block[12] in his Nobel prize address. Acetate is a sufficient starting material for the sequence shown in the Figure. With the background of our Figure we are prepared to examine some of the clinically important aspects of the control of cholesterol synthesis. It is now known that in mammals dietary cholesterol

will inhibit liver cholesterol synthesis both in intact animals and in liver slices. In their studies Siperstein and Fagan[13] showed the site of feed-back inhibition to be between beta-hydroxy, beta-methyl glutarate and mevalonate. The authors also demonstrated that a cell-free cholesterol synthetic system consisting of liver microsomes and the soluble fraction of liver plus appropriate media would also show such inhibition. When the dietary cholesterol was 5%, the incorporation of carbon 14 labeled acetate into cholesterol was reduced to 1% and 3% of the control in cell-free and liver-slice systems respectively. In contrast, the incorporation of labeled acetate into beta-hydroxy, beta-methyl glutarate was unaffected by dietary cholesterol, while in other studies mevalonate synthesis was inhibited about 97%. Pyridine nucleotide cofactors were not the limiting agent in this inhibition. The active cellular element carrying the enzyme sensitive to dietary cholesterol is evidently the membranous part of the microsome fraction as judged by removal of ribosomes from microsomal membranes with ethylenediaminetetracetic acid. The enzyme involved is beta-hydroxy, beta-methyl glutaryl reductase.

Cholesterol synthesis in hepatic tumors does not respond to such dietary feedback control,[14] nor does the intestine.[15] Fasting decreases both liver cholesterol synthesis[16] and fatty acid synthesis.[17]

THE GENERAL SCHEME OF CHOLESTEROL SYNTHESIS

Acetyl COA + Acetoacetyl CoA

Beta-hydroxy, beta-methyl glutarate

(B hydroxy B methyl glutarate)*

.....Site of dietary cholesterol inhibition[13]

.....Chlorphenoxyisobutyrate inhibition according to Avol et al.[28]

Mevalonate

ATP

Mevalonate-5′-PO_4

ATP

Mevalonate-5′-pyrophosphate

ATP

.....Atromid inhibition according to Azarnoff et al.[26]

CO_2

Δ^3 Isopentanol-5-pyrophosphate
condensation with one isoprene

Geranyl pyrophosphate (10 carbons)
condensation with one isoprene

Farnesyl pyrophosphate (15 carbons)
condensation of 2 farnesyl units

Squalene (30 carbons)
cyclization of squalene

Lanosterol
multiple rearrangements

Desmosterol

.....triparonol inhibition

Cholesterol

*In Siperstein's and Fagan's 13 system, the free compound and its COA derivative could not be incorporated into cholesterol; therefore, the biological compound may be a protein bound intermediate.

Figure

Intestine

The intestine is capable of cholesterol synthesis; early studies suggested that up to 18% of the plasma cholesterol came from the intestine.[18] Lindsay and Wilson recently demonstrated rather conclusively that the intestine delivers endogenously synthesized cholesterol into the intestinal lymph.[19] Rats were fed a 5% cholesterol diet which inhibited liver synthesis. Acetate C-14 injected intravenously appeared in *cannula*-diverted intestinal lymph, while blood activity remained zero. This appearance could not be due to biliary cholesterol since bile diversion from the test animal with bile restoration from a second animal gave the same results. Bile was necessary, however, for the maximal appearance of radioactivity into the lymph. When the intestinal lymph was allowed to drain into the circulatory system, blood radioactivity was appropriate for the dilution effect.

The site of cholesterol synthesis in the intestine was studied *in vitro* by Dietschy and Siperstein.[15] Lower small bowel slices incorporated acetate-C-14 into digitonin-precipitated sterols at greater rates than upper small bowel slices. Similar results were seen in the colon. The most active intestinal rates were still only one-fourth of the rate observed in the liver. The layer of gut wall most active in the synthesis was the layer of crypts of Lieberkuhn. Cholesterol feeding did not inhibit the synthesis; however, it was demonstrated that bile markedly inhibited the acetate incorporation into sterol. Above the ampulla of Vater there was active synthesis, while below, synthesis was reduced. A variety of experiments with bile perfusion confirmed this result. This result has pertinent applications to the clinical state of biliary obstruction where serum cholesterol increases. Most intestinal cholesterol synthesis probably is related to the turnover of epithelial cells.

Studies on the Site of Action of Chlorphenoxyisobutyrate

Chlorphenoxyisobutyrate was introduced by Thorp and Waring.[20] Most studies on this drug have been clinical in nature and relatively little is known about its mechanism of action. It was originally thought to require the presence of androgen; however, this is not true.[21] Many clinical studies have demonstrated a reduction of cholesterol from 15-20% and serum triglyceride from 30-40%, disappearance of xanthomas and retinal exudates, decreased plasma fibrinogen and reduced anticoagulant requirements.[21-24]

Atromid (chlorphenoxyisobutyrate and androgen) appears to affect chiefly the S_F 20-400 class of lipoproteins.[23] In a study of 14 patients with high cholesterol levels. Atromid reduced S_F 20-400 lipoproteins by 53% and S_F 0-20 by 4%. In contrast D thyroxin in the same patients decreased S_F 20-400 by 12% and S_F 0-20 by 21%. The high density lipoproteins were also affected by Atromid. Atromid increased the HDL-3 fractions by 60%. These studies suggest separate mechanisms for the two drugs and support the greater effect of Atromid on triglyceride levels.

The evidence on the cellular mechanism of action of chlorphenoxyisobutyrate is incomplete. Two studies contain data on the site of action. Azarnoff et al.[25] found that liver homogenates from cats eating a 0.2% clofibrate (ethyl chlorphenoxyisobutyrate) diet incorporated mevalonic acid-C-14 into cholesterol at only 20-40% of the rate of the control, a statistically significant decrease. In separate experiments C-14-O_2 production, lanosterol-C-14 and squalene-C-14 synthesis were all reduced by the drug, leading the authors to place the inhibition at the decarboxylation of mevalonic acid (Figure). These authors found increased liver weights. In contrast to Best and Duncan[26]

they found a decrease in total liver cholesterol as well as cholesterol concentration in spite of the increased liver weight. Equivocally decreased liver glycerides and increased liver phospholipids were observed. These changes correlate with the marked increase in liver lysosomes and mitochondria noted by Paget[27] in electron microscopic studies of chlorphenoxyisobutyrate-treated rats. Monkeys are said not to show such changes. Clofibrate may interfere with drug detoxification as indicated by the prolongation of hexobarbital sleep in rats. A most significant piece of evidence in this paper is related to the release of cholesterol and triglycerides from perfused rat livers. Triglyceride release was significantly reduced while cholesterol release was unchanged.

Another study related to mechanisms was that of Avoy et al.[28] who fed rats 0.3% chlorphenoxyisobutyrate or Atromid and found a 25% increase in liver weight, a 10% decrease in cholesterol concentration and a 30% decrease in plasma cholesterol levels. Acetate C-14 incorporation into liver-slice cholesterol was depressed 70%, while mevalonate-C-14 incorporation into cholesterol was not significantly reduced. Ketone body and triglyceride formation were not reduced, nor was intestinal cholesterol synthesis. *In-vivo* experiments were not as convincing. These results appear to conflict with Azarnoff et al.,[25] placing the block prior to mevalonic acid synthesis (see Figure). Such a site of inhibition would be similar to that of dietary cholesterol.

To summarize the meager evidence on the mechanism of chlorphenoxyisobutyrate, it appears that the drug partially blocks cholesterol synthesis prior to sequalene with no increase of toxic sterol intermediates.[22] In the plasma the decreased cholesterol is not in the principle cholesterol-bearing lipoproteins, the beta lipoprotein fraction, but rather in the pre-beta triglyceride-rich fraction. This would account for the greater efficacy of the drug in Types III and IV hyperlipidemias as suggested by Fredrickson et al.[10,11] Since the drug appears to block triglyceride release from the liver and since the liver probably makes endogenous triglyceride particles,[8] the mechanism may involve an inability to combine triglycerides with soluble beta lipoproteins or an inability to transfer such particles. The increased lysosome content may be significant in this regard. The results on triglyceride synthesis in liver are not at all convincing and further work on fatty-acid and triglyceride synthesis should be done.

Future Research

It is extremely important to establish the cellular mechanisms of drug action to ensure its use in a sensible fashion. With Atromid we know little about its effect on triglyceride synthesis. Even more poorly understood is the packaging of triglyceride with transport lipoproteins. Techniques are available and need to be used in basic cellular research on lipoprotein chemistry. In the meantime we need to establish the type of lipoprotein abnormality present in each patient before we embark on therapy. The use of Atromid or chlorphenoxyisobutyrate should be done with caution until we understand why it causes hepatic hypertrophy in rats.

Case Reports

Case 1

A 50-year-old negro female was admitted October 11, 1967, with a chief complaint of syncope secondary to antihypertensive medication. Previous problems evaluated in this hospital included: hypertension, aortic stenosis and cerebrovascular accident of undetermined age.

Renal workup negative except for narrowing of inferior branch of right renal artery noted on angiogram.

Physical Examination

Positive findings included: prominent arcus senilis, grade I arteriosclerotic changes on funduscopic examination, grade II systolic murmur and residual weakness of left arm and shoulder.

Pertinent Laboratory Findings

Cholesterol
- 5/10/67 268 mg.%
- 5/16/17 308 mg.%
- 10/11/67 415 mg.%
- 10/14/67 370 mg.%
- 10/31/67 315 mg.%
- 11/ 2/67 327 mg.%
- 11/ 3/67 330 mg.%

Phospholipids
- 10/14/67 243 mg.%

Triglycerides
- 10/14/67 74 mg.%

Protein Bound Iodine
- 5/18/67 7.6 mg.%

T_3 resin
- 5/16/67 30.2%
- 10/27/67 27.5%

I_{131} Uptake
- 10/14/67 14.5%

Glucose Tolerance Test normal.

Serum protein electrophoresis
- elevated gamma globulin fraction

Probable hyperlipoproteinemia class: Type II

Case 2

A 46-year-old white male was admitted August 3, 1967, with chief complaint of dull chest pain radiating to both arms. Past history was not informative.

Physical Examination

Positive findings included only arcus senilis.

Electrocardiogram revealed acute inferior myocardial infarct.

Laboratory Results

SGOT—Rise confirmed diagnosis of myocardial infarct.

Cholesterol
- 8/22/67 290 mg.%
- 8/26/67 340 mg.%
- 9/ 1/67 345 mg.%
- 9/25/67 390 mg.%

Protein Bound Iodine—4.6 mg.%

T_3 resin—25.3%

I_{131} Uptake— 3 hr. 4.5%
24 hr. 16.5%

Triglyceride 64 mg.%

Glucose Tolerance Test—Normal

Son, Jeffrey, (age 19) Cholesterol 230 mg.%

Probable classification unclear; may be secondary Type II.

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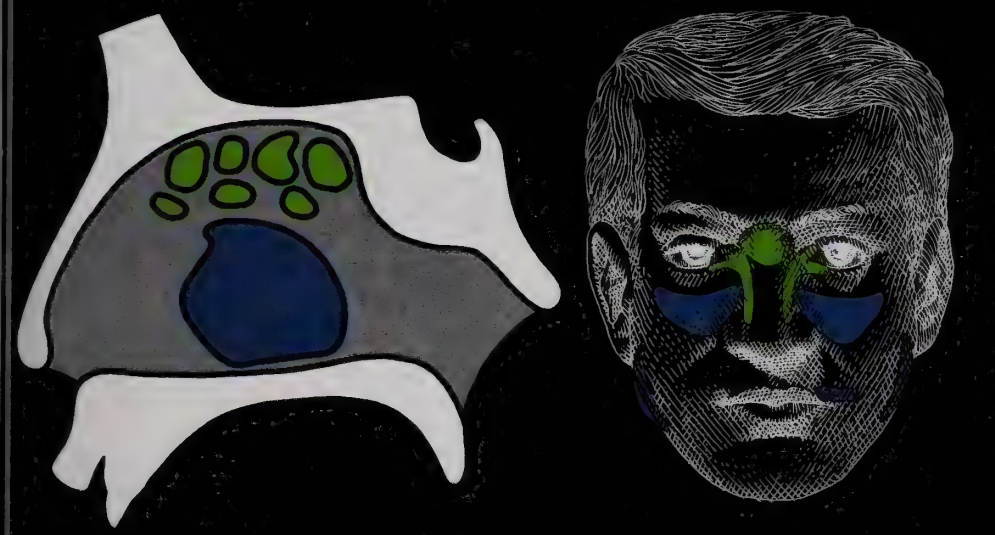
The mind is like the stomach. It is not how much you put into it that counts, but how much it digests.—Albert Nock

Sources of sinus headache



REGION OF SENSATION

FRONTAL SINUS—headache localized over the frontal region, commonly beginning in the morning. Eyes painful to touch, may be slight swelling over eyes, puffy eyelids.
SPHENOID SINUS—most difficult to diagnose. Headache or sense of pressure over vertex. May be pain in ear or mastoid region.



MAXILLARY SINUS—headache and tenderness under eyes at top of cheekbones, usually starting in early afternoon. Possible swelling of cheek. Pain in jaw and back teeth.
ETHMOID SINUS—headache, tightness in upper part of bridge of nose and well down its sides. Pain, deep-seated behind the eyes and in inner corners of the eyes.



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Book Reviews

For a good book is a solid thing.
—Pearl Buck Walsh

THE PREVENTION OF HIGHWAY INJURY—Edited by Melvin L. Selzer, M.D., Paul W. Gikas, M.D., and Donald F. Huelke, M.D. Published by Highway Safety Research Institute, The University of Michigan, Ann Arbor. 1967. Price $6.50. Copies may be obtained either from the University of Michigan Publications Distribution Service, East University Avenue, Ann Arbor, Michigan 48104, or from Clearinghouse, Code 410.14, U. S. Department of Commerce, Springfield, Virginia 22151.

Research into the causes and prevention of highway death and injury is small in amount compared to that done on cancer, cardiovascular disease and many other disorders of less consequence to the population. But an encouraging trend is developing. Among manifestations of this wholesome trend was the recent establishment in December 1965 of the Highway Safety Research Institute at the University of Michigan. One of its significant steps was to sponsor, with the University of Michigan Medical School, a Symposium on "The Prevention of Highway Injury" held April 19-21, 1967. This volume brings together the papers presented at that symposium.

The transcripts of the two opening addresses are worth the price of the book. About how many Welcoming Addresses can you say that? One was given by Robert L. Hess, Director of the Institute. No bland pabulum of welcome was this. He laid it on the line about the staggering size of the problem and the measures that will be required to come anywhere near solving it. The second talk was delivered by Dr. William G. Haddon, Director of the National Highway Safety Bureau. This was no polite high-sounding bit of fluff either; the pressing need for more and better truly scientific research in the field was highlighted. Grim fact, stern exhortation and wise philosophy pervade the entire paper.

The Symposium did not attempt to cover all the causes of collisions, but handled some of the most important, particularly those of direct or indirect medical interest. Four sections divide the material into groupings as follows: The Alcoholic Driver, Vision and Medical Impairment, Biomechanics (of injury) and The Second Collision. The papers are, without exception, by recognized authorities. There is gathered here in one volume much material which is otherwise scattered in many and varied sources, some not easily available. Much of it is fascinating, almost all is thoroughly reliable. A great deal will be new to the physician and at variance with what he sees in the popular and para-medical press, which is unfortunately his only usual source of knowledge on the subject of traffic safety. Here is the authentic source-material, not the filtered, "interpreted", and too often inaccurate rewrites.

In addition to having a particular interest in traffic safety, I happened to attend this Symposium and I unhesitatingly recommend this book. It will help the doctor-reader to an intelligent understanding of some of the major causes of death and injury related to the ubiquitous automobile. And it will give him much that will be useful in advising patients about medical factors that affect the driving task.

John H. Rosenow, M.D.
Minneapolis, Minnesota

CARDIOVASCULAR PHYSIOLOGY—By Robert M. Berne, M.D. and Matthew N. Levy, M.D. Published by C. V. Mosby Company, St. Louis, 1967. Price: $10.75.

The preface to this book contains the usual statement that it is designed primarily for the medical and graduate student. It is one of a series on human physiology and does not cover certain areas of cardiovascular physiology, such as hematology, blood coagulation, renal, hepatic or pulmonary circulation.

Although the 242 well-illustrated pages contain a wealth of information, the undergraduate student may be well advised to retain his allegiance to one of the established textbooks of physiology. The serious graduate student, too, will find this book deficient in many aspects. Some of the presentations are by necessity, or by the author's preference, quite inadequate. The role of calcium in muscle contraction is mentioned in one sentence only. I failed to find any mention of serotonin. In the discussion of the conduction system of the heart one misses the Stannius' ligatures or reference to O. Loewi's elegant classical experiments which established acetylcholine as the depressor substance.

The emphasis in this short book is on function and regulation. The descriptions and concepts are clearly defined and always to the point. The reader is referred mainly to review articles which were selected for the comprehensiveness of their bibliographies.

However, in a book of this type, one would like to find a short but up-to-date chapter on methods of hemodynamic measurements, especially blood flow, tissue perfusion and pressures.

In short, the book lacks breadth for the beginner—and depth for the graduate student of cardiovascular physiology.

H. Wilhelm Heupel, M.D., Ph.D.
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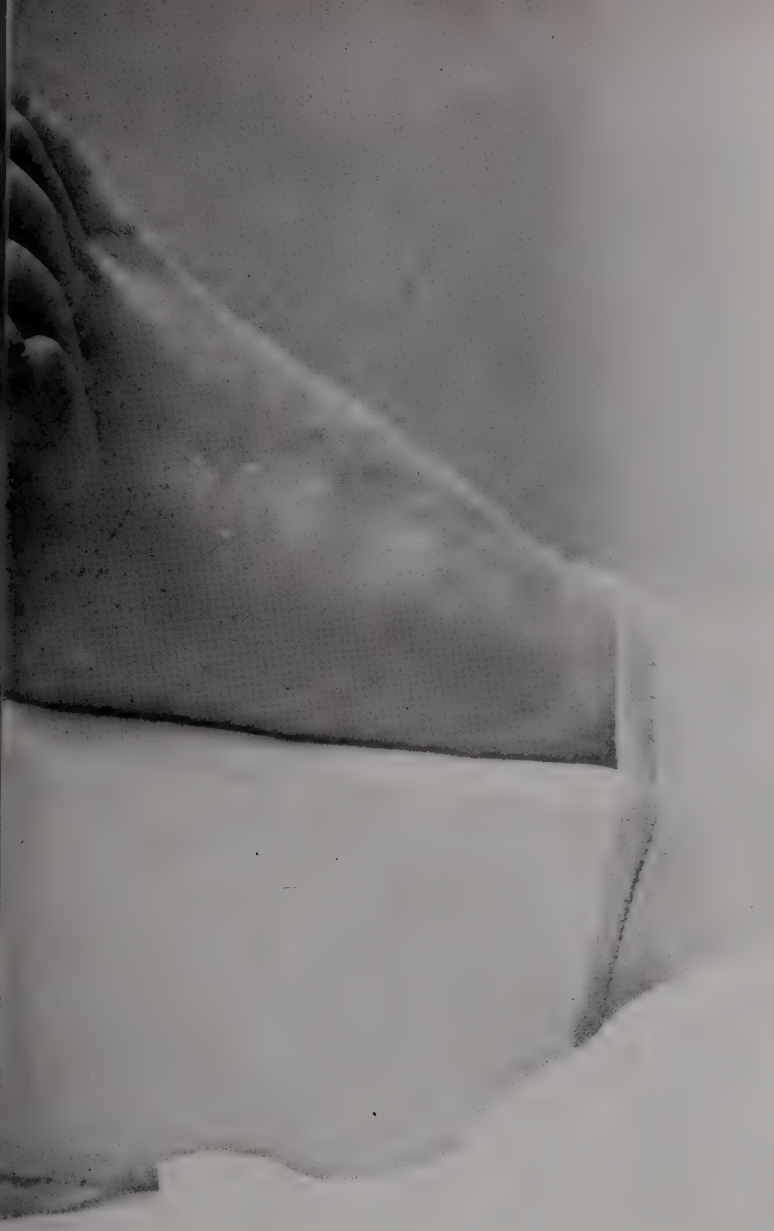
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Contraindications: History of sensitivity or severe intolerance to aspirin or meprobamate.

Warnings: USE IN PREGNANCY: Safety for use during pregnancy or lactation has not been established; therefore, it should be used in pregnant patients or women of childbearing age only when the physician judges its use essential to the patient's welfare.

Precautions: Keep out of reach of children. Not recommended for patients 12 years old or less. Carefully supervise dose and amounts prescribed, especially for patients prone to overdose themselves. Excessive prolonged use of meprobamate may result in dependence or habituation in susceptible persons—as alcoholics, ex-addicts, severe psychoneurotics. Withdraw gradually after prolonged high dosage to avoid possibly severe withdrawal reactions including epileptiform seizures. Warn patients of possible reduced alcohol tolerance. If drowsiness, ataxia or visual disturbances (impairment of accommodation and visual acuity) occur, reduce dose. If symptoms persist, caution patients against operating machinery or driving. After meprobamate overdose, prompt sleep, reduction of blood pressure, pulse and respiratory rates to basal levels, and hyperventilation are reported. Give cautiously to patients with suicidal tendencies. Treat attempted suicide (has resulted in coma, shock, vasomotor and respiratory collapse and anuria) with immediate gastric lavage and appropriate supportive therapy (CNS stimulants and pressor amines as indicated).

Side Effects: Ethoheptazine and aspirin may occasionally cause nausea, vomiting, epigastric distress, and rarely dizziness. Overdosage may result in CNS depression (drowsiness and lightheadedness) or CNS stimulation and salicylate intoxication (requires induced vomiting or gastric lavage, specific parenteral electrolyte therapy for ketoacidosis and dehydration, and observation for hypoprothrombinemic hemorrhage [usually requires whole blood transfusions]). Meprobamate may cause drowsiness, ataxia and rarely allergic or idiosyncratic reactions. These reactions, sometimes severe, can develop in patients receiving only 1 to 4 doses who have had no previous contact with meprobamate. Mild reactions are characterized by urticarial or erythematous maculopapular rash. Acute nonthrombocytopenic purpura with petechiae, ecchymoses, peripheral edema and fever have been reported. If allergic reaction occurs, meprobamate should be stopped and not reinstituted. Severe reactions, observed very rarely, include angioneurotic edema, bronchial spasms, fever, fainting spells, hypotensive crises (1 fatal case), anaphylaxis, stomatitis and proctitis (1 case) and hyperthermia. Treat symptomatically such as with epinephrine, antihistamine and possibly hydrocortisone. A few cases of leucopenia, usually transient, have been reported following continuous use. Rarely, cases of aplastic anemia (1 fatal case), thrombocytopenic purpura, agranulocytosis, and hemolytic anemia have been reported; almost always, in the presence of known toxic agents.

Composition: 150 mg. meprobamate, 75 mg. ethoheptazine citrate and 250 mg. aspirin per tablet.

Wyeth Laboratories **Philadelphia, Pa.**

When pain evokes anxiety and tension, thereby heightening patient discomfort, a simple analgesic may only touch on part of the problem.

This single-prescription, non-narcotic product, however, usually provides effective analgesia *and* helps put the patient's mind at ease.

The Cocovores

The most resolute pioneer of a natural way of life was August Engelhart. He held the remarkable view that the coconut was the only natural food for a man, since he was descended from the apes. In future he would eat nothing but this: in the morning the coconut milk, at midday the fresh pulp and at supper the dried pulp. The community that rallied to his new cure ate entirely according to the prescriptions of the master. Every other type of food was forbidden to the "Cocovores," as they called themselves. To make this natural life more realistic Engelhart demanded that his followers should go naked. This demand was difficult to comply with in Germany, on account of the police regulations and the excessive winter cold. The little band then decided to emigrate to the tropics, the original home of the human race. Money was collected; a small South Seas atoll with coconut palms and the beautiful name of Kakabon was purchased.

A chosen number of Cocovores retired here and formed the "Noble Kakabon Community," with the aim of ennobling themselves on the island through nakedness and an unremitting diet of coconuts. However, Engelhart turned out to be a tyrant who enforced Draconian laws. It was forbidden to wear any article of clothing; and although the island was full of magnificent fruit trees and bushes, only coconuts were to be eaten. The plentiful fish and shellfish to be found in every bay of the island were taboo. A prison and torture chambers were erected to punish those who infringed the law. This severity was justified by the high ideals aimed at by the coconut-nobility. Unfortunately this ideal human type was never allowed to see the light of the world: the Cocovores all died from undernourishment and severe punishment in the midst of plenty. When the British occupied the island during the first world war they found a single survivor, the coconut prophet himself. He still observed the severe ritual of his coconut diet, although his legs were swollen from starvation, and his body was covered with ulcers. As a German he was taken to a prison camp where he soon died.*

*H. S. Glasscheib: The March of Medicine, 1964.

Shakespeare and Medicine

Shakespeare knew a lot of medicine and he portrays seven doctors in his plays. Dr. Caius, of course, in the Merry Wives of Windsor is a figure of fun who threatens to perform a feminizing operation on Sir Hugh Evans if he dares interfere again with his love affairs. The English doctor in Macbeth refers to the curing of scrofula by the royal touch. Samuel Johnson was thus "touched" by Queen Anne, but with little effect. The Englishman had a wise Scottish colleague. He took one look at Lady Macbeth and said, "This disease is beyond my practice." Dr. Butts in Henry VIII, the physician in King Lear, Cornelius in Cymbeline, and Cerimon in Pericles are all good character parts and good doctors. Through them Shakespeare shows an astonishing familiarity with medical and anatomical terms and with the history of medicine. He mentions in different plays a whole heap of drugs, herbs, narcotics, and aphrodisiacs. He gave vivid pictures of the ravages of a score of different diseases and he indicated the treatment then fashionable for most of them.*

*Harvey Graham: A Doctor's London, 1952. See next issue of Minnesota Med.



Abstracts, Briefs and Commentaries

DISAPPEARING FOOT PULSES

"In the majority of cases the organic basis (of disappearing foot pulses) is complete occlusion of the major arteries to the lower extremity." "It is not unusual, however, for pronounced clinical symptoms to be due to stenosis within these arteries." "In such cases there are often multiple stenoses of atheromatoses origin." Atheromatous plaques may be found at the bifurcation of major arteries.

Patients with isolated stenosis in a major artery of the lower extremity may have palpable pulses at rest which disappear during exercise. "A special type of arterial stenosis with this clinical symptom is the isolated stenosis at the bifurcation of the common femoral artery." Operative treatment was recommended by De Weese et al.[1] in such cases.

Case Report

Case 1.

A 40-year-old engineer had had diabetes for eight years, and for six months he had had symptoms of intermittent claudication when walking a short distance. Blood pressure was normal. Pulsations were present on both legs over the dorsalis pedis and the posterior tibial arteries at rest. On the right side these pulsations disappeared after exercise but returned in a few minutes. Arteriography was normal in both extremities except for a distinct stenosis at the bifurcation of the right superficial and deep femoral arteries.

At operation an arteriotomy was done over the stenosed area extending down the deep artery. A large obstructing atheromatous plaque causing marked stenosis was excised, and the bifurcation was enlarged by a vein patch graft. Three months later the patient had no claudication and the pulses were strong after exercise.

Case 2.

A 54-year-old woman with intermittent claudication had good pulses at rest; but they disappeared after exercise. Arteriogram showed moderate stenosis at the beginning of the deep femoral artery on the left side.

An operation similar to that in Case I was performed. A large stenosing plaque was found on the dorsal aspect of the bifurcation. Two months after surgery there was marked improvement of symptoms and the pulses were present after exercise.

Discussion

There are numerous reports of patients with arterial stenosis who have palpable pulses. Thomas (1922) first described the disappearance of the pedal pulses during exercise. Some authors attribute the disappearance to

arterial spasm. It is generally thought that the decrease in pulsation is due to redistribution of blood flow to the working muscles with relative decrease of distal pulsive flow. It has also been suggested that the disappearance is an exaggerated normal response.

It is thought that a severe stenosis is necessary to produce a distal fall of blood pressure at rest. A plaque at a bifurcation may be adequate. Surgical procedures may vary; there may be reconstruction, endarterectomy, and/or by-pass.

Stenosis of the femoral artery should be suspected in a patient with claudication despite the presence of distal pulses at rest. Disappearance of pulsations during exercise confirms the diagnosis. Arteriography should give the final proof, but the degree of stenosis cannot always be determined by a frontal projection.

Stanley R. Maxeiner, Sr., M.D.
Minneapolis, Minnesota

Reference

1. De Weese, J. A.: Pedal Pulses Disappearing with Exercise: a Test for Intermittent Claudication. New Engl J Med 262:1214, 1967.

Drickson, Ingvar, Departments of Orthopedic Surgery and General Surgery, University of Uppsala, Sweden. Disappearing Foot Pulses, Report of Two Cases with Isolated Stenosis at the Bifurcation of the Common Femoral Artery. Acta Chir Scand 133:333, 1967.

PITFALLS IN THE CLINICAL USE OF CENTRAL VENOUS PRESSURE

Twenty patients had hourly examinations for urine output, hematocrit, heart rate, arterial blood pressure, skin perfusion, central venous pressure, and blood volumes.

Although the series is biased, there were nine of 20 patients in whom the central venous pressure was misleading as an evaluation of the hemodynamic state. Blood volumes were helpful, but when used alone were misleading in four of 20 patients. Central venous pressure may also be misleading because of the following factors: (a) the unique relationship between left ventricular end-diastolic pressure and left ventricular function, (b) the fact that central venous pressure is a better indicator of right ventricular than left ventricular function, (c) hypovolemia, per se, which may result in decreased left ventricular function, (d) mechanical dysfunction of catheter for various reasons, and (e) other etiologic disease of chest or heart affecting venous pressure.

Conclusion—Blood volume and central-venous-pressure determinations are most helpful when used concomitantly.

Jerome Grismer, M.D.
Minneapolis, Minnesota

Brisman, R., Parks, L. C. and Benson, D. W.: Pitfalls in the Clinical Use of Central Venous Pressure. Arch Surg 95:902, 1967.

FINGER INJURY CAUSED BY PAINT SPRAY GUN

Modern grease guns which inject lubricant or paint through a small jet are capable of puncturing the skin and spreading subcutaneously some distance from the point of entry. Grease is toxic and produces a severe local reaction; even great swelling, pain and fever.

A male, 22, while adjusting a paint spray gun got his finger over the nozzle and received an injection of a small amount of paint. One hour later the finger disclosed a puncture 1/3 millimeter in diameter. There was no pain or inflammatory reaction. In view of the previous reports of similar accidents

with grease, operative exploration was performed. White paint was present in the surrounding tissues. All tissue that seemed likely to undergo necrosis was excised. The wound was left open.

The following day the entire finger was swollen and inflamed; the patient was febrile and complained of intense pain. On further exploration the paint was found to have spread more widely than found during the less radical surgery. The wound was closed loosely to permit drainage. Some necrotic tissue sloughed off. Healing required three weeks. One year later there was some atrophy and some impairment of sensation but no loss of movement of the joints of the finger.

In this instance the injected paint contained toxic ingredients, whiting and five other substances that could have toxic effects.

Comment: In some cases where grease was injected with insignificant trauma, extensive toxic inflammatory reaction and necrosis followed. Radford (Surgical Clinics of North America 43, 1277) reported 23 cases in which grease was injected and caused severe toxic inflammatory reactions.

The very high pressure causes the injected material to follow the fascial planes well beyond the point of entrance. The author recommends that the entire course of the injected material be explored.

Stanley R. Maxeiner, Sr., M.D.
Minneapolis, Minnesota

Spec Ivar: Finger Injury Caused by Paint Spray Gun. From the Department of Surgery, Länslasaretlet, Hässleholm, Sweden.

PATTERNS OF ARTERIOSCLEROTIC LESIONS OF THE LOWER EXTREMITY

The author analyzed the arteriograms of 321 lower extremities in 189 patients. The entire arterial tree (lower abdominal aorta, iliacs, femorals, popliteals, posterior tibials, and peroneal vessels including pedal branches) was visualized. Two types of patients were studied: diabetics with atherosclerosis and non-diabetics with atherosclerosis.

Eight major patterns were discernible, the majority of which had diffuse or extensive lesions. Pathologic data indicate that the atherosclerotic lesions are usually far more advanced than the arteriograms would suggest, especially in the diabetic patient. Of the various patterns, more than 50% of the femoral-popliteal lesions were associated with aorto-iliac disease.

Comment: Very nice angiograms are presented. The need for complete aorto-iliac definition is well documented. The author employed "general anesthesia," but this has not been necessary in the reviewer's experience of retrograde "flushing" to visualize the aorto-iliac tree.

Jerome Grismer, M.D.
Minneapolis, Minnesota

Haimovici, H.: Patterns of Arteriosclerotic Lesions of the Lower Extremity. Arch Surg 95:918, 1967.

FACTORS INFLUENCING LIMB SURVIVAL AFTER FEMOROPOPLITEAL RECONSTRUCTION

The results of reconstructive arterial surgery deserve further emphasis. These authors dealt with the following prognostic factors: (1) indication for reconstruction expressed as degree of ischemia, (2) effect of failed reconstruction on the level of amputation, (3) diabetes mellitus, (4) age, and (5) presence of recent femoropopliteal thrombosis.

Ninety-two patients (96 limbs) had primary femoropopliteal reconstruc-

tions (29 saphenous vein grafts, 34 thromboendarterectomies, 31 plastic grafts, and two arterial homografts). There were 10 secondary reconstructions because of primary failures (two vein grafts, two thromboendarterectomies, five plastic grafts, and one homograft).

Degrees of ischemia were divided into (1) claudication only (32 limbs); (2) rest pain, numbness, paresthesia (39 limbs); (3) skin necrosis (33 limbs).

Adverse factors on reconstruction were age, diabetes mellitus, type of reconstructive procedure, recent thrombosis, and degrees of ischemia. As expected, the limbs with claudication only fared the best. Vein graft reconstruction was more successful at five years than were the other procedures.

Although the patency rate for all reconstructive procedures progressively declined over five years, limb survival remained high considering the three classes: 87%, 69%, 54% respectively. A high operative mortality (26%) was associated with reconstructive procedures for acute thrombosis.

Comment: Although reconstructive surgery has definite advantages, this report again dramatizes the generalized arteriosclerotic problem—its progressive course, and the deleterious effect of operation in certain instances. The over-all clinical and economic factors relative to the patient must be evaluated prior to reconstruction.

Jerome Grismer, M.D.
Minneapolis, Minnesota

Couch, N. P., Wheeler, H. B., Hyatt, D. F., Crane, C., Edwards, E. A. and Warren, R.: Factors Influencing Limb Survival after Femoropopliteal Reconstruction. Arch Surg 95:163, 1967.

Poseidonius: Raw-Food Advocate

The first to propose a systematic and deliberate preference for raw food was the well-known mathematician, astronomer, and Stoic philosopher, Poseidonius, who lived about 100 B.C. Both Pompey and Cicero were his pupils, and they acclaimed his wisdom. Poseidonius maintained that the human being could survive without cooking, if he were prepared to increase the work of his jaws and digestion. Cooking was only a substitute for chewing and a very poor substitute at that. Man, who possessed an oral cavity with a set of teeth, salivary glands and a tongue, needed neither a miller nor a cook, pots and pans, or even the worst of all evils, a wife standing by the oven; but a healthy human body which would serve as his own miller and cook and could attend to these tasks better and more efficiently.

Poseidonius practised what he preached: throughout his life he chewed roots, ears of corn, beans and peas, and attained the respectable but by no means extraordinary age of eighty-four.*

*H. S. Glasscheib, M.D.: The March of Medicine, 1964.

Man in this moment of his history has emerged in greater supremacy over the forces of nature than has ever been dreamed of before . . . There lies before him, if he wishes, a golden age of peace and progress. All is in his hand. He has only to conquer his last and worst enemy—himself.—Winston Churchill, 1950

Tobacco

Some things are much better eschewed than chewed; tobacco is one of them.—George D. Prentice

Photography

If you look like your passport photo—you need the trip.—Jacob Braude: Speaker's Encyclopedia

When the emotionally impaired patient pays an office call...

She asks for your help, but just can't seem to follow through on your advice.

When not at your office, she's constantly on the phone: can't sleep, headache, G.I. upset.

She often seeks a physical explanation for her distressing emotional state.

She's excessively apprehensive; demands much more of your nurse's attention.



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- Mellaril helps control the most frequent symptoms: marked tension, agitation, apprehension, restlessness, hypermotility
- Mellaril often alleviates anxiety-induced somatic complaints
- Mellaril frequently helps strengthen emotional resources
- Mellaril helps the patient maintain realistic contact with environment, closer harmony with family

Contraindications: Severely depressed or comatose states from any cause, and in association with or following MAO inhibitors; severe hypertensive or hypotensive heart disease.

Precautions: Hypersensitivity reactions (e.g., leukopenia, agranulocytosis) and convulsive seizures are infrequent. Pigmentary retinopathy has been observed where doses in excess of those recommended were used for long periods of time. May potentiate central nervous system depressants, atropine, and phosphorus insecticides. Where complete mental alertness is required, administer the drug cautiously and increase dosage gradually. In addition, orthostatic hypotension (especially in female patients) has been observed. Epinephrine should be avoided in treatment of drug-induced hypotension.

Side Effects: Pseudoparkinsonism and other extrapyramidal disorders are infrequent; drowsiness, especially in high doses early in treatment, may occur; nocturnal confusion, dryness of the mouth, nasal stuffiness, headache, peripheral edema, lactation, galactorrhea, and inhibition of ejaculation are noted on occasion; photosensitivity and other allergic skin reactions may occur but are extremely rare.

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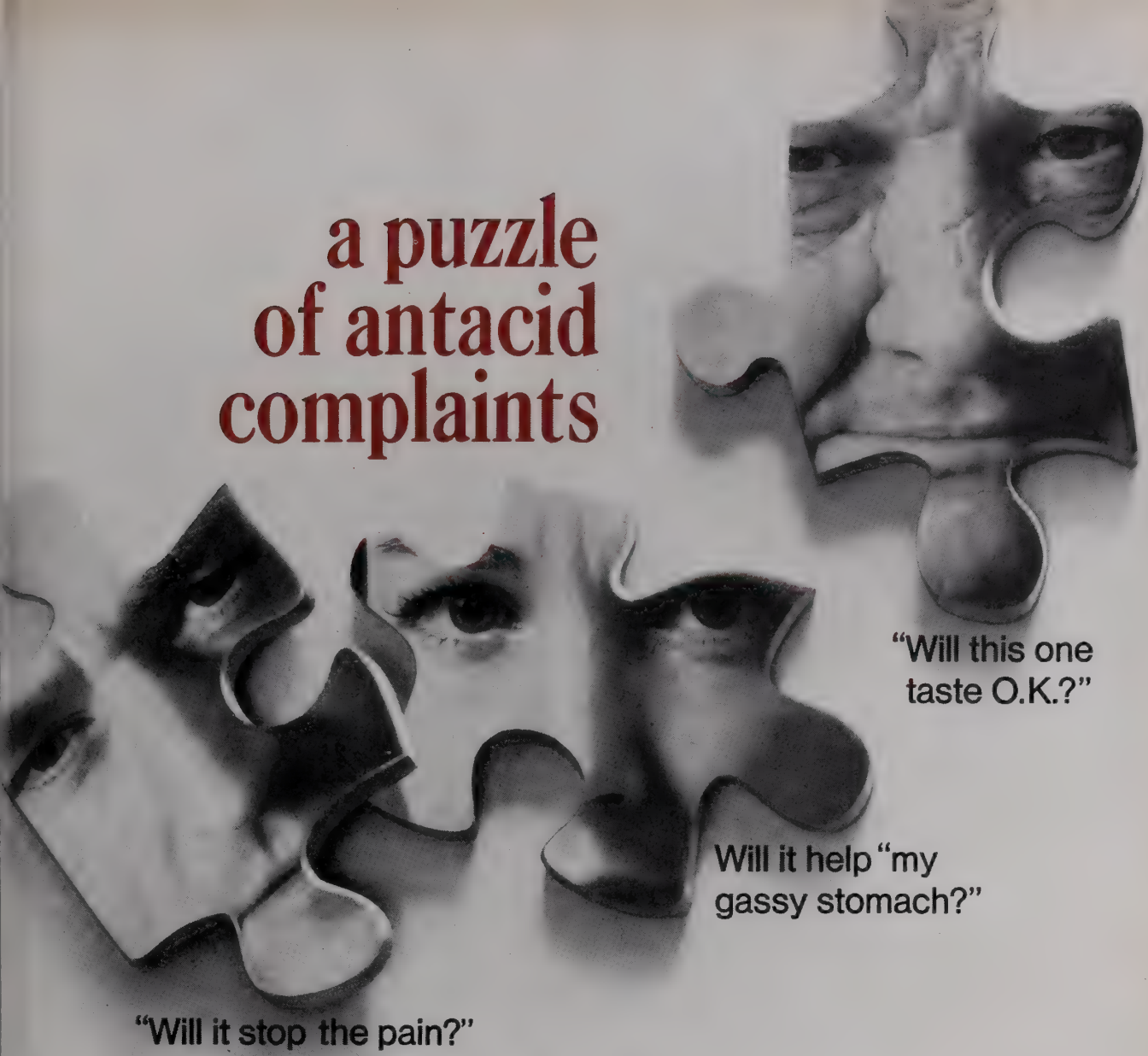
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Prescribing Information: Composition: Each white, beveled, compressed tablet contains: Quinine Sulfate 260 mg. and Aminophylline 195 mg. **Contraindication:** QUINAMM is contraindicated in pregnancy because of its quinine content. **Precautions:** Aminophylline may produce intestinal cramps in some instances, and quinine may produce symptoms of cinchonism, such as tinnitus, dizziness, and gastrointestinal disturbance. Discontinue use if ringing in the ears, deafness, skin rash, or visual disturbances occur. **Dosage:** One tablet upon retiring. Where necessary, dosage may be increased to one tablet following the evening meal and one tablet upon retiring. **Supplied:** Bottles of 100 and 500 tablets.

References: 1. Shuman, C.: Am. J. Med. Sci., 225:54, 1953. 2. Perchuk, E., et al.: Angiology, 12:102, 1961. 3. Rawls, W., et al.: Med. Times, 87:818, 1959.

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Mylanta®

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with the two most widely prescribed antacids: aluminum and magnesium hydroxides.

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in 87.5% of 104 patients after a total of 20,459 documented days of therapy.[2]

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References: 1. Hoon, J. R.: Arch. Surg. *93*:467 (Sept.) 1966.
2. Danhof, I. E., Personal communication.

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For a cold, NTZ® Nasal Spray provides rapid relief of nasal symptoms. Relief starts with the first spray which opens the inferior part of the common meatus. A second spray, a few minutes later, will shrink the turbinates to help provide sinus drainage and ventilation. Dosage may be repeated every three or four hours as needed, for temporary relief of symptoms. NTZ is well tolerated but overdosage should be avoided.

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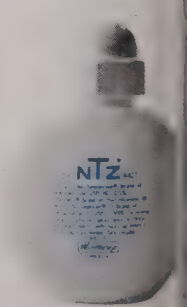
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Special Article

Humor in Scientific Medical Writing*

RICHARD L. REECE, M.D.
Minneapolis, Minnesota

HUMOR, BY TURNING a timeworn subject upside down to glimpse the underside, may stimulate readers by giving them a new view. For example, I turn to Cecil and Loeb's *Textbook of Medicine,* where Fuller Albright is introducing "Diseases of Ductless Glands" by telling us what he, "the author," will *not* do:

". . . he will not delve into the earliest beginnings of endocrinology which had as their *raisons d'etre* such ends as the procurement of manpower safe for a harem, the salvaging of a male soprano for the choir, the increased palatability that a rooster attains when he turns into a capon, and so forth."[1]

What has Albright done? For one thing, he commands his material well enough to be unorthodox, even irrelevant. For another, he opens in such a way to lure us to the meat of the matter. By telling us what he will *not* do, Albright prods us into going on to find out what he *will* do.

Catching His Eye

The physician with too much to read often saves time by scanning introductions. Writers who want their material read appreciate this, and they set out to hook the scanner early. To catch his eye, they may use a quick opener with a surprise twist.

If you are not acquainted with this technique, I invite you to listen to this opener to "Champagne-Cork Injury to the Eye" in *The Lancet.*[2]

"Since the invention of the champagne cork towards the end of the 17th century, there appear to have been very few records of injuries to the eye from flying champagne corks. In fact we have been able to find only one article, by Tiburtius (1962), on the subject. Cooper (1859), who wrote the first authoritative textbook on eye injuries, makes no mention of such an occurrence, although he describes numerous other bizarre misfortunes. It is interesting that the inventor of the champagne cork, a Benedictine monk

*Address before the American Medical Writers' Association, September 21, 1967.

by the name of Dom Perignon, was himself blind, although the cause is not known."

Having tantalized their reader with that historical tidbit, the authors proceed to the heart of their article. Later, in their discussion, they keep his attention with this advice:

These injuries can be avoided by care in opening the bottle. The Comité Interprofessionel du Vin de Champagne has published a handbook which describes how to serve it. A napkin should be held over the cork and the neck of the bottle while the wire is being undone, and the cork is gently eased off with the bottle pointing away from the face. There should be no "pop" but merely a sigh. White gloves may be worn but are not essential.

Adapting to His Habits

Humor can serve as bait for that quick-eyed creature—the Summary Skimmer. Instead of gulping down whole journals, he skims through summaries—searching for something which suits his taste.

Had he been darting through the *New England Journal of Medicine* recently, he would have pulled up short when he read the following summary. The authors, three radiologists, are closing a report on pulmonary lycoperdonosis—a disease caused by inhaling puffball spores.

"In the interest of preventive medicine it is suggested that puffballs be gathered while young and, thinly sliced, sautéd in butter with a touch of garlic and a pinch of thyme. They are delicious prepared in this manner."[3]

Here the writers captured their readers by trolling for them. They probably knew their title—Lycoperdonosis—might snare curious, conscientious, and conventional readers, but they were after speed-reading backenders. To catch them, they dangled out the rear a morsel fit for a connoisseur.

Word Watching for Him

Then there is word watching. It is a good way of drawing fun-seeking readers into expository flow. At one time or another, most of us have poked fun at medical names or terms. It's safe, it's harmless, and it helps relieve frustrations over long, latinized words.

To illustrate word watching, I have an article from the *Journal of the American Medical Association*. Its author, Doctor Howard H. Steel, an orthopedic surgeon, is wrestling with the problem of naming toe nail and finger nail lesions which resemble Garlic-Cloves. He has already discarded the term "Steel's Nails" because it lacks modesty, and he has rejected "Hyperkeratotic Polypoid Ungual Fibroma" as stark and inhumane. Here he is leading up to his final name—"Garlic-Clove Fibroma."

"What is needed is a warm, homey sort of name. Numerous precedents exist for the use of a familiar descriptive term, a comparison with some household object . . . the silverfork deformity; the funnel breast; nutmeg liver; oat-cell carcinoma; scalloped ribs; cauliflower ear; portwine stains; doughnut pessary; sago spleen; current-jelly stool . . . coffee ground vomitus; and bringing up the rear, the grapes of wrath of the proctologist."[4]

The author's intent is clear. He wants to entertain his reader by playing on the shapes and sounds and meanings of names. Whatever his intent, I think he succeeds, for articles like his are likely to be read.

Showing Him the Gray Zones

That hazy middleground between where science stops and where art starts provides fertile soil for humor. A sense of humor, after all, is closely akin to a sense of proportion. This next specimen comes from a pathologist's pen. Doctor Sigmund Wilens is lamenting his inability to give clinicians precise scientific reasons why patients die.

"For 30 years as a practicing pathologist, I have been trying to supply the answers to that perpetual question, 'Why did he die?' It has been most fatiguing . . . until we have a bit more understanding about causes of life . . . the causes of death are apt to remain mysterious. . . . One can only speculate about the cause-of-death phraseology of the future. Will it be 'lysosomal derangement,' 'intracellular enzymatic arrest,' 'generalized impermeability of basement membranes,' 'paralysis of the reticuloendothelial system,' or 'cytoimmunological insufficiency.' "[5]

As a fellow pathologist, I find Doctor Wilens' commentary amusing. He presents a practical problem, tells of the limitations of science, and points up the incongruity of it all

by concocting a string of scientific immeasurables.

Identifying With Him

Probably the surest form of humor is to give fun to others by making fun of yourself (yourself being like other selves). All of us make mistakes, but we rarely record them in print. To publicly recount errors is novel, and therefore it has impact. Confession can make an ordinary report memorable.

Doctor Richard Asher[6] sets the stage by titling his paper "A Woman with Stiff-Man Syndrome." Having enticed us with that, he informs us that while reading about a "curious condition" he realized it was:

". . . a clear description of a case of a woman whose extraordinary spasms had puzzled me ten years previously. Luckily the ward sister remembered her name; the notes were traced and revealed the lady had continued to suffer from 'hysterical spasm'* which had disabled and deformed her. . . . I wish to report his case, (a) because I made the diagnosis ten years late; (b) because it appears to be the first case of stiff-man syndrome in England; (c) because it shows that syndromes are sometimes labelled hysterical for no better reason than they have not yet been officially described; even in this case where the patient's hysterical spasms were so titanic (and that is not a misprint for tetanic) that they bent a Smith Peterson nail and fractured a steel plate and screws."[6]

I have quoted Doctor Asher's report at some length because it shows how effective humor, especially self-depreciating humor, can be. First, Doctor Asher catches the reader's eye with his paradoxical title; then he appeals to his sympathy by confessing he diagnosed a strange disease as hysteria (haven't most of us?); and then he cleverly plays "titanic" against "tetanic" to show the magnitude of his mistake and to etch on the reader's mind a dramatic aspect of the disease.

Appealling to His Intellect

Mention of the word "titanic" brings to mind a piece by Joseph Garland, who recently retired as editor of the *New England Journal of Medicine*. In the following editorial—"Wordupmanship, No Less"[7] he shows his bent for wit, that felicitous form of humor which is part perception, part ingenuity, part joining of seemingly unrelated things. Doctor Garland is having his go at the uses and abuses of the suffix "ship," particularly whether it should be appended to the word "relation."

He closes in this fashion.

"The case in favor of relation and against relationship except in a restricted sense having thus been clearly presented and incontrovertibly proved, it may be pertinent to recall a luncheon-table conversation about the sinking of the Titanic that took place in the Harvard Club of Boston, on the anniversary of that melancholy event. 'I had relations on the Titanic,' one discussant modestly admitted. 'With whom?' was the spontaneous interrogation of his fellow Harvardmen, striving for their own scholarly version of one-upmanship."[7]

Helping Him to Grin and Bear It

Then there is satire, which is nothing more or less than a thinking man's humor. Satire has bite, but it isn't mean. It should give information and insight as well as provoke a smile as has been done by Clifton Meador,[8] a Markle Scholar in Academic Medicine, in describing "The Art and Science of Nondisease."

"In a review of the charts of patients referred to the Endocrine Division with a variety of diagnoses it became apparent that a large number also had no disease. They were not *just* healthy; they had specific nondisease . . . a nondisease exists when a specific entity is suspected but is not found."[8]

Doctor Meador is not indulging in idle gamesmanship. He is inviting readers, many of whom are undoubtedly referring physicians, to *think* the next time they diagnose an endocrine disease. For, as Doctor Meador points out: ". . . the treatment for nondisease is never the treatment for the corresponding disease entity. In this statement lies the ultimate value of the science of nondisease."

The Case for Humor

So far in this presentation, one person has been very much in the news—the reader. If a writer is going to be read (and I assume most of us want to be read), we had best keep the reader in mind. We must sympathize with

*Asher's original diagnosis.

him, anticipate his needs, inform him, and, if appropriate and in good taste, amuse him.

To me the case for humor is clear. It is personal, it is human, it is readable. If our journals are to be actively read, (there's that word again) rather than to passively gather dust as storehouses of facts, they need to be enlivened. Humor can help us pump a little humanity into the flood of medical articles that cascade off the presses.

I am not saying humor is invariably right. Doctors deal with disease, human distress, and death. These are matters not taken lightly. Also, they usually tackle scientific subjects; and science, almost anyone will grant, is a serious business. Medical scientists are expected to grind out facts. To present these in an entertaining fashion is often difficult and sometimes impossible. Medicine, then, calls for serious men saying serious things, in a responsible manner. I do hope, however, the writer will occasionally laugh at himself, amuse his readers when it helps to hold their attention, warm up his facts before he serves them, and use humor whenever it adds a touch of humanity. As as veteran practitioner of prose, Alistair Cooke of the *Guardian* of England, remarked while addressing the Annual Convocation of the Mayo Graduate School of Medicine: ". . . And let us not get too solemn about what is meant by humanity; it ought always to mean compassion; but it might also include humor, which dignifies the giver and the receiver and is an excellent medicine in itself."[9]

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Tuberculosis Symposium

An all-day symposium on Clinical Pulmonary Problems, sponsored by the Ramsey County Tuberculosis and Health Association, will be held Friday, April 19, 1968, at the St. Paul-Ramsey Hospital.

Sessions will begin at 8:30 A.M. with registration and run through to 5:30 P.M. No registration fee is being set, but there will be a charge for luncheon and dinner.

Featured speakers will be Averill Liebow, M.D., Professor of Pathology, Yale University School of Medicine, and John Rankin, M.D., Professor of Medicine, University of Wisconsin Medical School. Other faculty members will include full-time or clinical staff members from the Mayo Medical Center and from the corps of Twin Cities physicians.

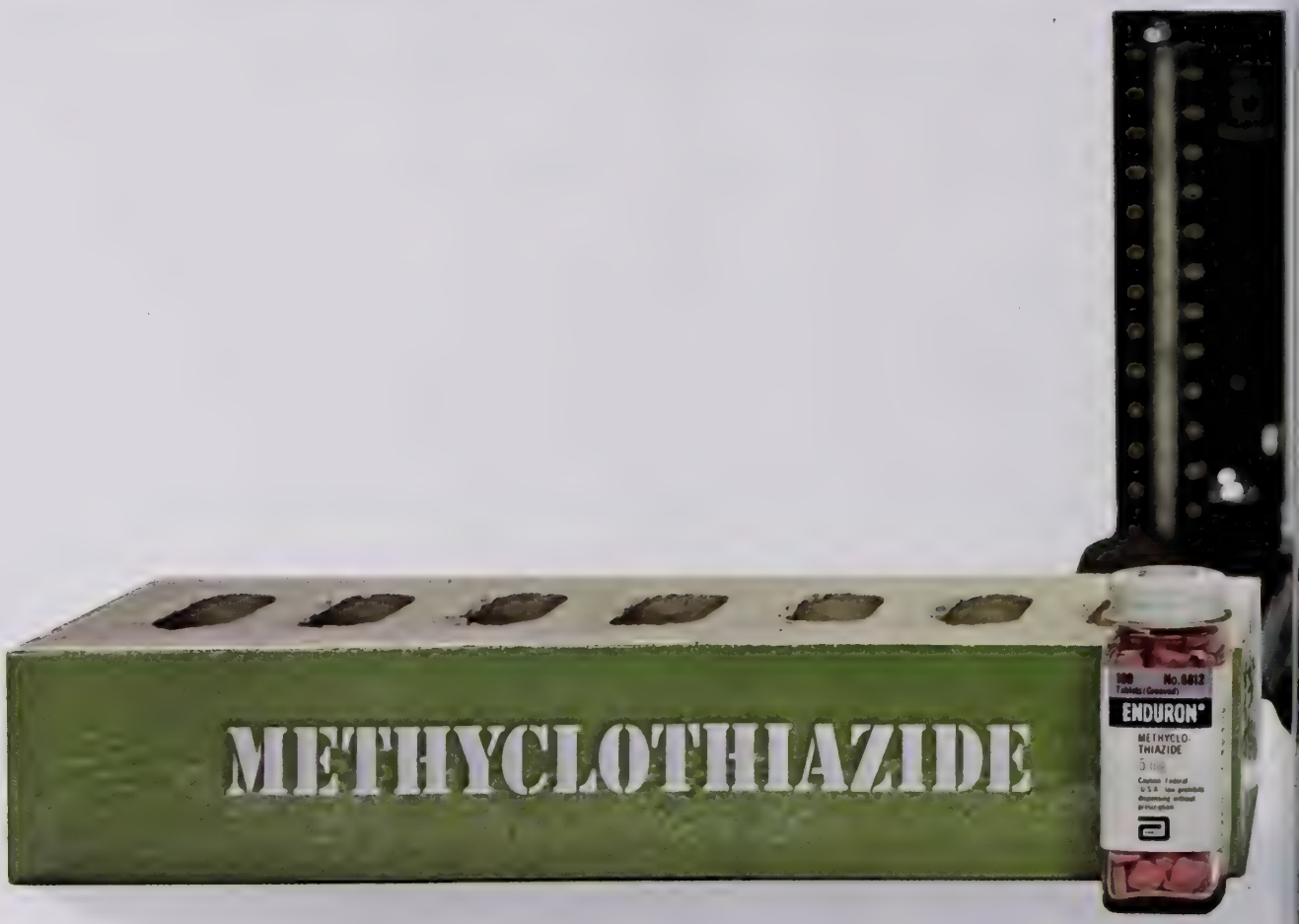
Dr. Liebow, an emminent authority on pulmonary work, will address the conference at a morning session and will be the featured dinner speaker, scheduled for 7:00 P.M. that night at the St. Paul Hotel. Reservations for dinner may be made by calling 224-4901, the TB Association office.

Abbott Antihypertensive Building Blocks

A simplified approach to the practical management of hypertension



Enduron: (methyclothiazide) A basic building block for mild hypertensives



Excellent day-long Na^+ output, yet easy on the K^+

Enduron provides an excellent starting therapy. Your patient's sodium excretion is greatly enhanced. Yet potassium loss is low.

The therapeutic action is smooth, and persists for a full 24 hours. With Enduron you can prescribe convenient once-a-day dosage without skimping your patients on day-long thiazide effectiveness.

Of course, as with all thiazides, supplemental dietary potassium should also be considered.

Use Enduron as a basic therapy in patients with mild to moderate hypertension. A single 5-mg. tablet each day is ample in most cases.

Once a day, every day

ENDURON

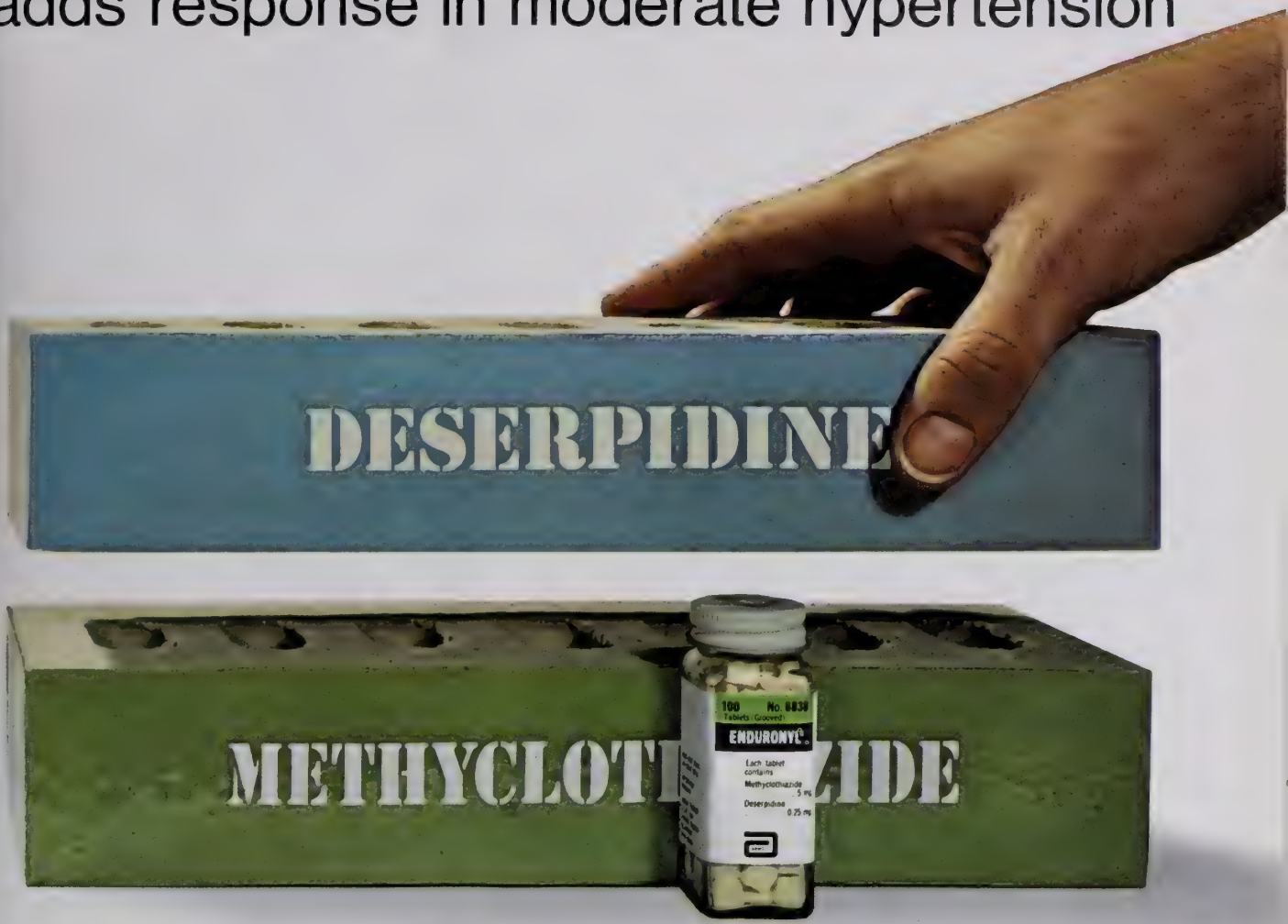
METHYCLOTHIAZIDE

MILD TO MODERATE TO SEVERE



See Brief Summary on final page of advertisement

Enduronyl: Its deserpidine component adds response in moderate hypertension



Less frequent rauwolfia side effects than with reserpine

When you wish to build further response, consider shifting to Enduronyl.

Enduronyl adds a building block of *deserpidine*. This is a purified rauwolfia alkaloid available only from Abbott. It adds good antihypertensive and tranquilizing activity. Yet its incidence of untoward effects, particularly lethargy and depression, is lower than with reserpine.

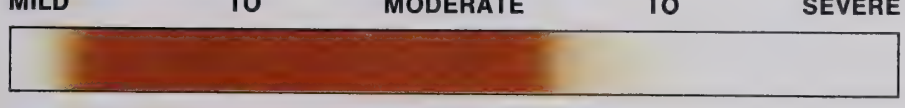
Enduronyl is available plain or Forte. The latter provides its variation where most helpful, by doubling the deserpidine.

Use Enduronyl for patients throughout the broad range of mild to moderately severe hypertension.

Once a day, every day

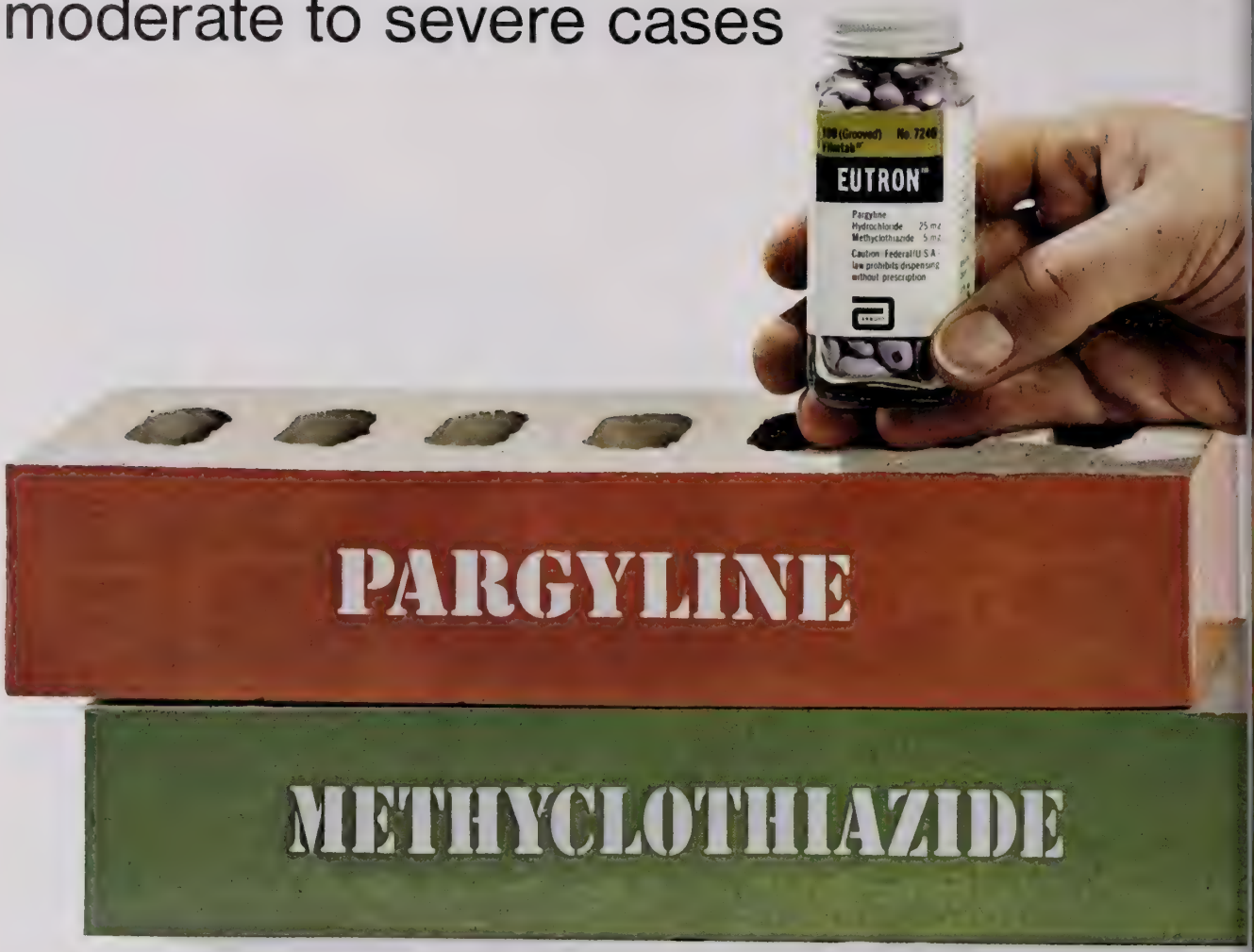
ENDURONYL®

METHYCLOTHIAZIDE 5 mg. with DESERPIDINE 0.25 mg. or (FORTE) 0.5 mg.



See Brief Summary on final page of advertisement

Eutron: A unique combination for handling moderate to severe cases



Affords almost uniform diastolic reduction in all body positions

Eutron lowers diastolic pressures nearly equally, whether your patient is standing up or lying down.

Thus, in clinical trials, average *standing* diastolic readings were reduced from 112 pre-treatment to 90 post-treatment; *sitting* from 115 to 95; and *recumbent* from 112 to 94.

Note that following Eutron, the diastolic reductions were nearly alike in all three body positions.

Use Eutron for managing your moderate to severe cases. Its building blocks enhance each other; hence lesser doses often suffice.

Once a day, every day

EUTRON™

PARGYLINE HYDROCHLORIDE 25 mg.
with METHYCLOTHIAZIDE 5 mg.

MILD TO MODERATE TO SEVERE



See Brief Summary on final page of advertisement

ENDURON® | ENDURONYL®

METHYCLOTHIAZIDE

Each tablet contains
Methyclothiazide 5 mg. with
Deserpidine 0.25 mg. or 0.5 mg.

Indications: Edema and mild to moderate hypertension (Enduron), and mild to moderately severe hypertension (Enduronyl). More potent agents, if added, can be given at reduced dosage.

Contraindications: Sensitivity to thiazides; severe renal disease (except nephrosis) or shutdown; severe hepatic disease or impending hepatic coma (hepatic coma due to hypokalemia has been reported in patients on thiazides). Do not use Enduronyl in severe mental depression, suicidal tendencies, active peptic ulcer, or ulcerative colitis.

Warnings: Consider possible sensitivity where there is history of allergy or asthma. If added potassium is indicated, dietary supplementation is recommended. Reserve enteric-coated potassium tablets for cautious use only when necessary, as they may induce serious or fatal small bowel lesions (stenosis with or without ulceration), cause obstruction, hemorrhage, and perforation often requiring surgery; discontinue them immediately if abdominal pain, distention, nausea, vomiting, or g.i. bleeding occurs. Neither Enduron nor Enduronyl contains added potassium.

Precautions: Use thiazides cautiously in severe renal dysfunction, impaired hepatic function or progressive liver disease; also in pregnancy (bone marrow depression, thrombocytopenia, and altered carbohydrate metabolism have been reported in certain newborn). In surgery, thiazides may reduce response to vasopressors, and increase response to tubocurarine. Antihypertensive response may be enhanced following sympathectomy. Watch for electrolyte imbalance (e.g., hyponatremia) in all patients. In hypokalemia (especially in digitalized patients) give supplemental potassium. In hypochloremic alkalosis, give supplemental chloride.

Use rauwolfias with caution in patients with history of peptic ulcer. Rauwolfias with anesthetics may produce hypotension and bradycardia. Discontinue Enduronyl two weeks before elective surgery. Consider vagal blocking agents during emergency surgery. In epilepsy, adjust anticonvulsant dosage. In electroshock, shorten stimulus strength and duration. In occasional patients with depressive tendencies, rauwolfias may precipitate severe mental depression that usually disappears when drug is stopped.

Adverse Reactions: Thiazide reaction include blood dyscrasias (thrombocytopenia with purpura, agranulocytosis, aplastic anemia); elevation of BUN, serum uric acid or blood sugar; anorexia, nausea, vomiting, diarrhea, headache, dizziness, paresthesia, weakness, skin rash, photosensitivity, jaundice, symtomatic gout, and pancreatitis. Cutaneous vasculitis in the elderly has been reported with other thiazides. Adverse effects with deserpidine are qualitatively similar to those with reserpine, but their incidence is lower. These include nasal stuffiness, abdominal cramps or diarrhea, nausea, headache, weight gain, reduced libido and potency, peptic ulcer aggravation, epistaxis, skin eruption, asthma in susceptible patients, electrolyte imbalance, excessive salivation, and a reversible Parkinson's syndrome. Excessive drowsiness, fatigue, weakness, and nightmares may signal mental depression. Thrombocytopenia, purpura, and a symptom manifested by dull sensorium, deafness, uveitis, glaucoma, and optic atrophy are rare allergic reactions to other rauwolfias. Hypotension from antihypertensive agents may precipitate angina attacks in susceptible individuals. Usually adverse reactions disappear when drug is withdrawn.

EUTRON™

Each tablet contains
Pargyline Hydrochloride 25 mg.
with Methyclothiazide 5 mg.

Indications—Moderate to severe hypertension.

Contraindications—Pheochromocytoma, paranoid schizophrenia, hyperthyroidism and advanced renal failure. Not recommended in malignant hypertension, children under 12, pregnant patients.

Do not use with: centrally or peripherally acting sympathomimetic drugs; foods high in tyramine (e.g., aged and natural cheeses); parenteral reserpine or guanethidine; imipramine, amitriptyline, desipramine, nortriptyline or their analogues; other monoamine oxidase inhibitors; methyldopa or dopamine; separate Eutron and these agents by two weeks.

Sensitivity to thiazides; severe renal disease (except nephrosis) or shutdown; severe hepatic disease; impending hepatic coma from thiazide-induced hypokalemia.

Warnings—Patients: 1. No other drugs (particularly "cold preparations" and antihistamines), cheese or alcohol without physician's consent. 2. Promptly report orthostatic symptoms, severe headache, other unusual symptoms. 3. Angina pectoris or coronary artery disease patients must not increase physical activity with improved anginal symptoms or well-being.

Physicians: 1. Use antihistamines, hypnotics, sedatives, tranquilizers and narcotics (meperidine contraindicated) cautiously in reduced doses. 2. Stop Eutron two or more weeks before elective surgery; in emergency surgery reduce premedication (narcotics, sedatives, analgesics, etc.) to 1/4 to 1/5; carefully adjust anesthetic dosage to patient response. 3. Use cautiously in advanced renal failure. 4. Pargyline may induce hypoglycemia. 5. Consider possible sensitivity reactions when a history of allergy or asthma is present. 6. If potassium is indicated, dietary supplement is recommended; enteric-coated potassium tablets may induce serious or fatal small bowel lesions (stenosis with or without ulceration), cause obstruction, hemorrhage, and perforation frequently requiring surgery; discontinue medication immediately if abdominal pain, distention, nausea, vomiting or gastrointestinal bleeding occurs; Eutron does not contain added potassium. 7. Possible systemic lupus erythematosus has been reported for thiazides.

Precautions—Pargyline: Use cautiously at reduced dosage: caffeine, alcohol, antihistamines, barbiturates, chloral hydrate, other hypnotics, sedatives, tranquilizers, narcotics. Periodically do urinalyses, blood counts, liver function tests, etc. Use with caution in liver disease. Watch for orthostatic hypotension, especially in impaired circulation (e.g., angina pectoris, coronary artery disease, cerebral arteriosclerosis); also, augmented hypotension in concomitant febrile illnesses. Reduce or discontinue if hypotension is severe. In impaired renal function watch for cumulative drug effects, elevated BUN and other evidence of progressive renal failure; withdraw drug if these persist. In surgery increased central depressant response (hypotension and increased sedative effect) can be controlled by (1) discontinuing at least two weeks prior; (2) in emergency surgery lowering dose of premedication; (3) when necessary, administering a vasopressor. Do not use in hyperactive and hyperexcitable patients. Pargyline may unmask severe psychotic symptoms where emotional problems pre-exist. Use cautiously in Parkinsonism, especially with antiparkinsonian agents. In prolonged therapy, examine for change in color perception, visual fields, fundi and visual acuity. Also, prolonged therapy has made certain patients refractory to nerve blocking effects of local anesthetics.

Methyclothiazide: Use cautiously in severe renal dysfunction, impaired hepatic function or progressive liver disease; also in pregnancy (bone marrow depression, thrombocytopenia, and altered carbohydrate metabolism have been reported in certain newborn). In surgery thiazide may reduce vasopressor response and increase tubocurarine response. Antihypertensive response may be enhanced following sympathectomy. Watch for electrolyte imbalance (e.g., hyponatremia). Give supplemental chloride if hypochloremic alkalosis occurs and supplemental potassium if hypokalemia occurs (especially in digitalized patients). Thiazides may decrease serum P.B.I. without signs of thyroid disturbance.

Adverse Reactions — Pargyline: Orthostatic hypotension and associated symptoms, mild constipation, fluid retention, edema, dry mouth, sweating, increased appetite, arthralgia, nausea, vomiting, headache, insomnia, difficult in micturition, nightmares, impotence, delayed ejaculation, rash, purpura, weight gain, hyperexcitability, increased neuromuscular activity and other extrapyramidal symptoms. Drug fever is extremely rare. Reduction in blood sugar and hypoglycemic effects are possible. Congestive heart failure has been reported in a few patients with reduced cardiac reserve.

Methyclothiazide: Blood dyscrasias (thrombocytopenia with purpura, agranulocytosis, aplastic anemia); elevation of BUN, blood sugar or serum uric acid (gout may be induced); anorexia, nausea, vomiting, diarrhea, headache, dizziness, paresthesia, weakness, skin rash, photosensitivity, jaundice and pancreatitis. Cutaneous vasculitis in elderly patients has been reported with other thiazides.

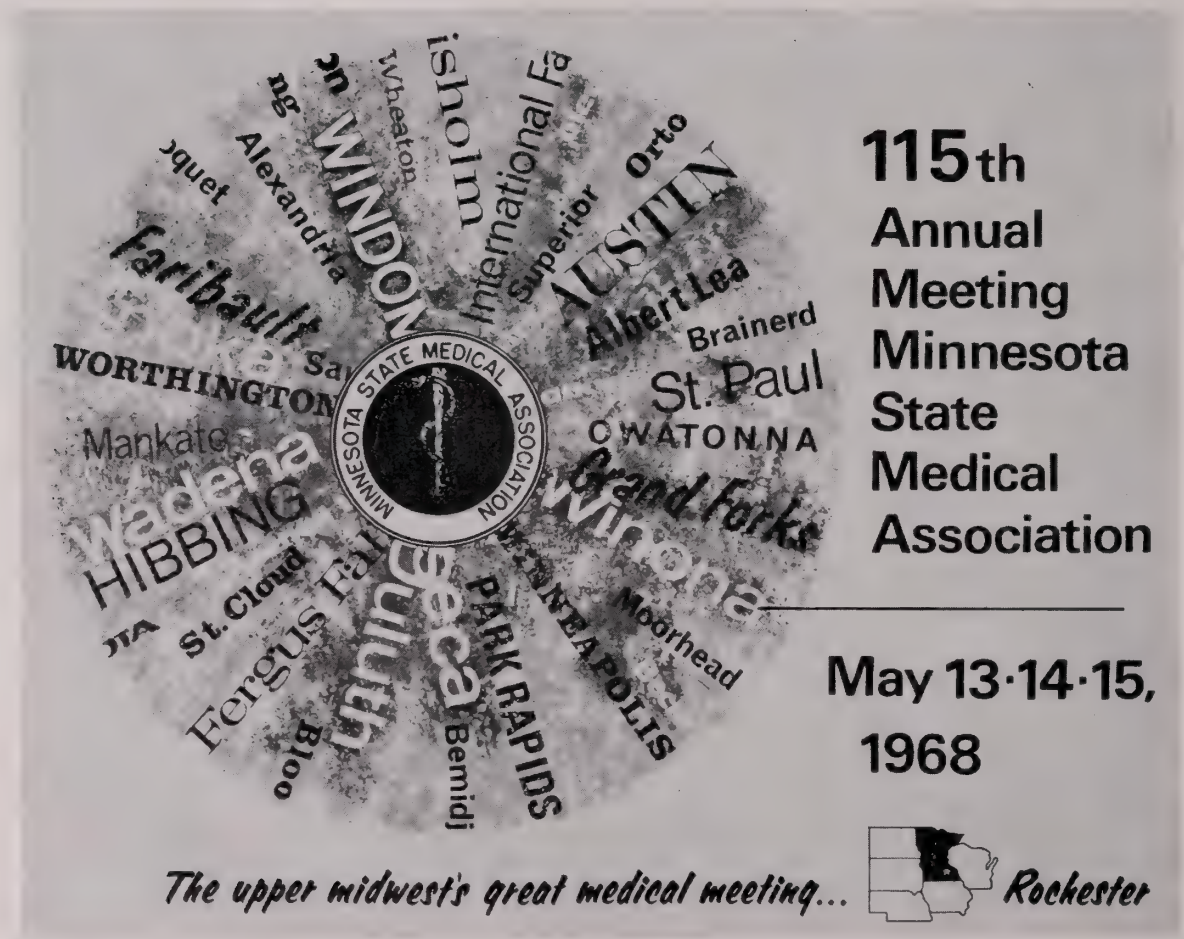
If side effects are severe or persist, reduce dosage or withdraw drug. 804438R

ABBOTT

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Annual Meeting

Rochester Will Host Our Annual Meeting



HEART, BLOOD, Bones, Shock, Sex will be the program headliners for the 115th Annual Meeting of the Minnesota State Medical Association, May 13, 14 and 15 in Rochester.

The Committee on Scientific Assembly notes that the treatment "in depth" of several major topics represents a new concept in programing, and speakers will include outstanding Minnesota physicians as well as a number of visiting dignitaries.

The scientific sessions, which will treat each of these topics from A to Z, are especially designed to be of practical interest to every physician.

Morning and afternoon sessions will be at the Mayo Civic Auditorium and will begin at 9:00 a.m. each day. It is expected that four-and-a-half hours of credit will be allowed for attendance at each full day by the American Academy of General Practice.

New concepts in the management of patients with acute myocardial infarction will be discussed at the opening session on Monday. Participants include: Doctor Edward A. Ryan, Duluth and Doctors Emilio R. Giuliani, Harold T. Mankin and Carlos E. Harrison, Jr., all of Rochester.

Doctor Norman E. Shumway, Thoracic Surgeon of Stanford University Medical School, Palo Alto, will give the principal address at the morning session. He will also act as leader at a Round Table Discussion Luncheon on Medicine and Religion.

The Monday afternoon session on blood will feature an address by Doctor Harry S. Jacob entitled "Mechanisms of Hemolysis in Hemolytic Anemia." Doctor Jacob is currently at Tufts University Medical School, Boston. Beginning July 1, 1968, he will be Hematologist and Associate Professor in the Department of Medicine at the University of Minnesota School of Medicine. Other participants are: Doctors Robert A. Green, Program Chairman on Blood, James L. McKenna, Howard L. Horns, and F. Bruce Lewis, all of Minneapolis; and Murray Silverstein and Joseph M. Kiely of Rochester. These physicians will all participate in rotating group subjects on a variety of topics concerned with disorders of the blood, with an exchange of questions and answers between them and participants in small groups.

To conclude the afternoon there will be a panel made up of these authorities to conduct a major question and answer period from the entire group in some specific areas of blood diseases.

Attendance at this session will provide physicians the opportunity to become better acquainted with new medical school faculty member Doctor Jacob.

Doctor Richard C. Lillehei, Professor of Surgery, will serve as chairman for the program of Shock on Tuesday, May 14, at 9:00 a.m. Speakers and their subject titles for the program on shock are:

Wesley J. Spink, M.D., Minneapolis—"Pathogenesis and Management of Endotoxin Shock"

William J. Martin, M.D., Rochester—"The Choice of Antibiotics in Management of Bacteremia and Shock"

Vincent J. Collins, M.D., Chicago—"The Prophylaxis of Shock"

Richard C. Lillehei, M.D., Minneapolis—"Monitoring of Patients in Shock"

Doctor Collins is Chief of the Department of Anesthesiology at Cook County Hospital, Chicago. He will also act as leader for a Round Table Discussion Luncheon on Local Anesthesia in Management of Injuries to the Extremities.

Physicians will have an opportunity to "meet the chiefs" at the 11:00 a.m. session on Tuesday morning. Recent additions to the University of Minnesota Medical School faculty and staff will be introduced by Dean Robert B. Howard. There will also be an opportunity at later Round Table Discussion Luncheons for physicians to discuss with the "chiefs" changes in medical education, including proposed changes in the medical school curriculum geared to family practice.

The following "chiefs" will be introduced at this session:—

John S. Najarian, M.D.
Professor and Head, Department of Surgery

Richard V. Ebert, M.D.
Professor and Head, Department of Medicine

John J. Sciarra, M.D.
Professor and Head, Department of Obstetrics and Gynecology

Michael Paparella, M.D.
Professor and Head, Department of Otolaryngology

John H. Westerman, Director
University Hospitals

Types of bone disease, reaction of bone to trauma, tumors, fractures, tissue response to trauma—all aimed toward the physician in family practice—will be presented at the 2:00 p.m. session on Tuesday. Doctor Harry B. Hall, Minneapolis, Chairman of this session, announces the following participants in a program series to be called "Bone Decisions by the Decade:"

Edward L. Salovich, M.D., Minneapolis
Leonard O. Langer, Jr., M.D., Minneapolis
Richard H. Jones, M.D., Minneapolis
H. Wilson Godfrey, M.D., Minneapolis
Harry B. Hall, M.D., Minneapolis
S. Hartley Calin, M.D., Minneapolis

At 4:30 three panelists will discuss "Diagnosis and Treatment of Benign and Malignant Tumors of the Blood." They are:—

John C. Ivins, M.D.—All of Rochester
David C. Dahlin, M.D.
Harry F. Bisel, M.D.

A wide variety of individual discussions under the title "Sex" will be conducted at the opening session Wednesday, May 15, at 9:00 a.m. Co-chairmen for this session are Doctors Maurice J. Martin and Richard M. Steinhilber, both of Rochester. Specific subjects will be treated on the basis of the practice-oriented setting—in terms of counseling, marital-sexual conflicts, adolescence and sex. The emphasis will be on normal, rather than abnormal, situations. The panel will keep its formal remarks to a minimum with emphasis on audience participation.

The traditionally popular round table luncheons scheduled for Monday and Tuesday noon will deal with a variety of topics of current interest to physicians. Round table topics include: medicine and religion, use of the gastric camera, family practice, philosophy of transplants, dermatology, the Keogh bill, heart, blood and anesthesiology.

The House of Delegates will convene Sunday, May 12, at 2:00 p.m. and again on Monday, May 13, at 7:30 p.m. Delegates are advised to note this change in time for the second session, traditionally held Tuesday morning.

The New Members, County Officers and Delegates Dinner is scheduled for Sunday, May 12, at 6:00 p.m. Reference committees will meet at 8:00 p.m. following the dinner. Many of the scientific and non-scientific committees of the Association have scheduled 7:30 breakfasts, during the session, and physicians are urged to consult their official program for exact time and location of specific committee meetings.

The annual Minnesota State Medical Association banquet is scheduled for 7:00 p.m., Tuesday, May 14, and will be preceded by the president's reception at 6:00 p.m.

The NUHOPE-AMPAC members will hold their annual dinner on Monday, May 13.

The Committee on Scientific Assembly is pleased to announce that this year's scientific and technical exhibits will be particularly outstanding. Physicians are urged by the committee to visit the exhibits and express their appreciation to the technical exhibitors whose annual participation at our meetings has helped to make the perennially excellent scientific sessions possible. Ample time to visit the exhibits will be provided between scientific sessions. Additional annual meeting information will appear in the next issue of MINNESOTA MEDICINE and in the monthly NEWSPAGE.

The official program and registration cards will be mailed to all physicians.

Twins?

Raynaud's disease and chilblains are Tweedledum and Tweedledee.—Osler

A typical politician, when he comes to the parting of the ways, goes both ways.
—Jacob Brande: Speaker's Encyclopedia

Progress

Democracy is ever eager for rapid progress, and the only progress which can be rapid is progress down hill.—*Sir James Jeans*

b.i.d.

The sensible schedule that covers the patient day and night

If your objective in the use of a broad-spectrum antibiotic is prolonged action, with high blood levels, then you know why b.i.d. DECLOMYCIN is considered to be a sensible dosage schedule.

The maintenance dosage of DECLOMYCIN can be kept at this convenient schedule because of its unusually high effective blood and tissue levels.

The b.i.d. dosage of DECLOMYCIN gives you the comfortable assurance that the patient is well-covered, *day and night.*

In clinical practice, blood levels produced by a therapeutic dose of DECLOMYCIN are high, prolonged, and effective; because of high serum binding and slow renal clearance. And if there's a broader susceptibility pattern of organisms, we've yet to see it.

There is no need to give higher daily dosage than 300 mg b.i.d., except in venereal diseases and Eaton Agent pneumonia.

DECLOMYCIN®
DEMETHYLCHLORTETRACYCLINE

Lederle

Prescribing information on next page.

b.i.d. The sensible schedule that covers the patient day and night

DECLOMYCIN Demethylchlortetracycline should be equally or more effective therapeutically than other tetracyclines when the offending organisms are tetracycline-sensitive.

Contraindication: History of hypersensitivity to demethylchlortetracycline.

Warning—In renal impairment, usual doses may lead to excessive accumulation and liver toxicity. Under such conditions, lower than usual doses are indicated, and, if therapy is prolonged, serum level determinations may be advisable. A photodynamic reaction to natural or artificial sunlight has been observed. Small amounts of drug and short exposure may produce an exaggerated sunburn reaction which may range from erythema to severe skin manifestations. In a smaller proportion, photoallergic reactions have been reported. Patients should avoid direct exposure to sunlight and discontinue drug at the first evidence of skin discomfort. Necessary subsequent courses of treatment with tetracyclines should be carefully observed.

Precautions—Overgrowth of nonsusceptible organisms may occure. Constant observation is essential. If new infections appear, appropriate measures should be taken. In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment.

Side Effects—Gastrointestinal system—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin—maculopapular and erythematous rashes. A rare case of exfoliative dermatitis has been reported. Photosensitivity; onycholysis and discoloration of the nails (rare). Kidney—rise in BUN, apparently dose related. Transient increase in urinary output, sometimes accompanied by thirst (rare). Hypersensitivity reactions—urticaria, angioneurotic edema, anaphylaxis. Teeth— dental staining (yellow-brown) in children of mothers given this drug during the latter half of pregnancy, and in children given the drug during the neonatal period, infancy and early childhood. Enamel hypoplasia has been seen in a few children. If adverse reaction or idiosyncrasy occurs discontinue medication and institute appropriate therapy.

Average Adult Daily Dosage: 150 mg q.i.d. or 300 mg b.i.d. Should be given 1 hour before or 2 hours after meals, since absorption is impaired by the concomitant administration of high calcium content drugs, foods and some dairy products. Treatment of streptococcal infections should continue for 10 days, even though symptoms have subsided.

In the treatment of syphilis a dosage schedule of a total of 12 to 18 Gm. given in equally divided doses over a period of 10 to 15 days should be followed. Close follow-up observation of the patient is recommended, including appropriate laboratory tests, since demethylchlortetracycline has not had adequate evaluation in all stages of syphilis. Spinal fluid examination should be included as part of this follow-up.

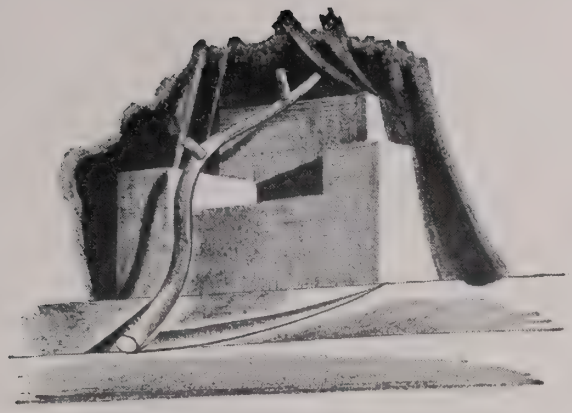
Acute gonococcal anterior urethritis in males has been treated effectively with a single dose of 600-900 mg. of DECLOMYCIN Demethylchlortetracycline. Individuals unable to tolerate large single doses due to gastrointestinal side effects may be treated with 150 mg. every 6 hours for a minimum of 4 doses or 300 mg. every 12 hours for a minimum of 2 doses. Females should be treated with a dosage of 150 mg. every 6 hours or 300 mg. every 12 hours until a cure is effected.

Primary Atypical Pneumonia (Eaton Agent): The average adult daily dosage is 900 mg. in 3 divided doses for six days.

LEDERLE LABORATORIES, A Division of American Cyanamid Company, Pearl River, N.Y.

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In Memoriam

God's finger touched him, and he slept.—Tennyson

ARTHUR W. IDE, M.D.

Dr. Arthur W. Ide, 92, St. Paul surgeon, died February 11. Born in Creaton, Iowa, he obtained his medical education at the University of Michigan.

Dr. Ide joined the staff of the Northern Pacific Hospital at Brainerd in 1905, and later became chief surgeon and moved to St. Paul in 1921. He remained chief surgeon until he retired in 1943.

He was a member of the Ramsey County Medical Society and the American Medical Association and a 50 Club and Life Member of the Minnesota State Medical Association.

He is survived by two sons, one of whom is Dr. Arthur W. Ide, Jr., of Minneapolis.

PETER BALEISIS, M.D.

Dr. Peter Baleisis, 51, who had practiced medicine in North Minneapolis for the past thirteen years, died suddenly January 14. He graduated from the University of Dusseldorf, Germany, in 1948 and came to this country two years later joining the staff of St. Joseph's Hospital in South Bend, Indiana. In 1954 he became associated with the Broadway-Suburban Clinic in Minneapolis.

He was a member of the American Medical Association, the Minnesota State Medical Association, the Minnesota Academy of General Practice, and the Hennepin County Medical Society.

Dr. Baleisis is survived by his wife, a son and a daughter.

LESTER R. PARSON, M.D.

Dr. Lester R. Parson, 76, Elbow Lake physician, died in his sleep January 23. Born in Jackson County, Minnesota, Dr. Parson taught in rural schools when not farming. Later he attended the University of North Dakota for his premedical training and graduated from Rush Medical College in 1921. In 1923 he moved to Elbow Lake where he and his wife, Dr. Lillian Parson, practiced medicine until January, 1960, when Dr. Lester retired.

He was a member of the American Medical Association and the Park Region District and County Medical Society and was a Life Member of the Minnesota State Medical Association.

He is survived by his wife, a son and a daughter.

THOMAS O. YOUNG, M.D.

Dr. Thomas O. Young, 74, prominent Duluth physician, died February 2, in a Duluth hospital after a long illness. Born in LeRoy, he had been a Duluth resident for forty-three years. He graduated from the University of Minnesota Medical School.

A founder and first president of the Duluth Surgical Society, Dr. Young was on the surgical staffs of St. Mary's, St. Luke's and Miller Hospitals. He had been elected to the honorary medical staff of St. Mary's the day before his death.

He was a member of the St. Louis County Medical Society, the American Medical Association, the American College of Surgeons, the Society of Abdominal Surgery, the American Thyroid Society, the Academic Internationale of Medicine, and a Life Member of the Minnesota State Medical Association.

He is survived by his wife and three sons, two of whom are Dr. Hadley Young and Dr. Allen A. Young of Duluth.

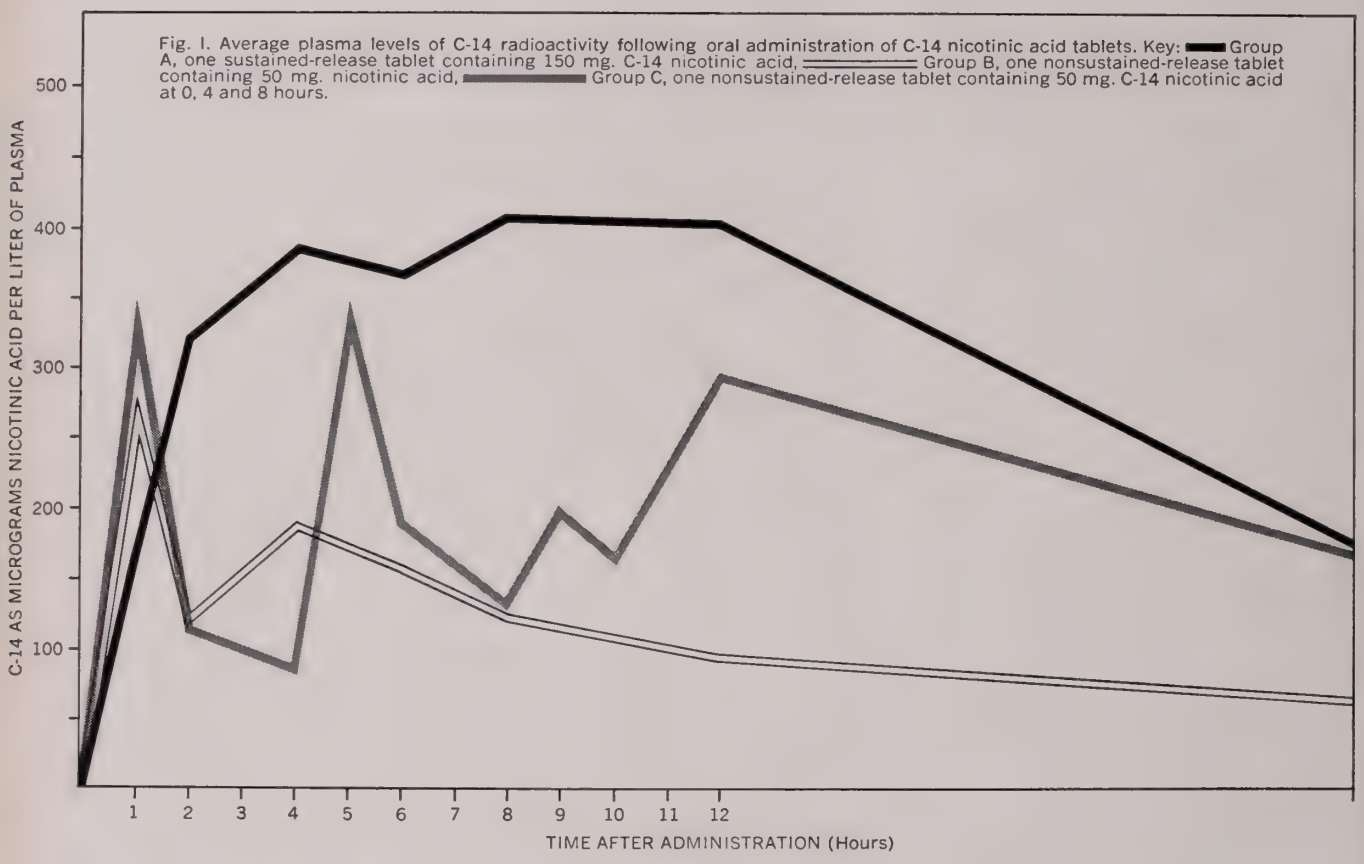
MORRIS H. SHERMAN, M.D.

Dr. Morris H. Sherman, 44, Minneapolis internist, died February 10, of a heart attack. Born in Minneapolis, Dr. Sherman graduated from the University of Minnesota Medical School in 1946.

He was a staff member of Mount Sinai Hospital and on the Board of Directors of the Minneapolis Talmud Torah. Dr. Sherman was also a member of the American Medical Association, the Hennepin County Medical Society and the Minnesota State Medical Association.

He is survived by his wife, a daughter and two sons.

Sustained circulatory, respiratory and cerebral stimulation for the





(fewer absent doses by absent-minded patients)

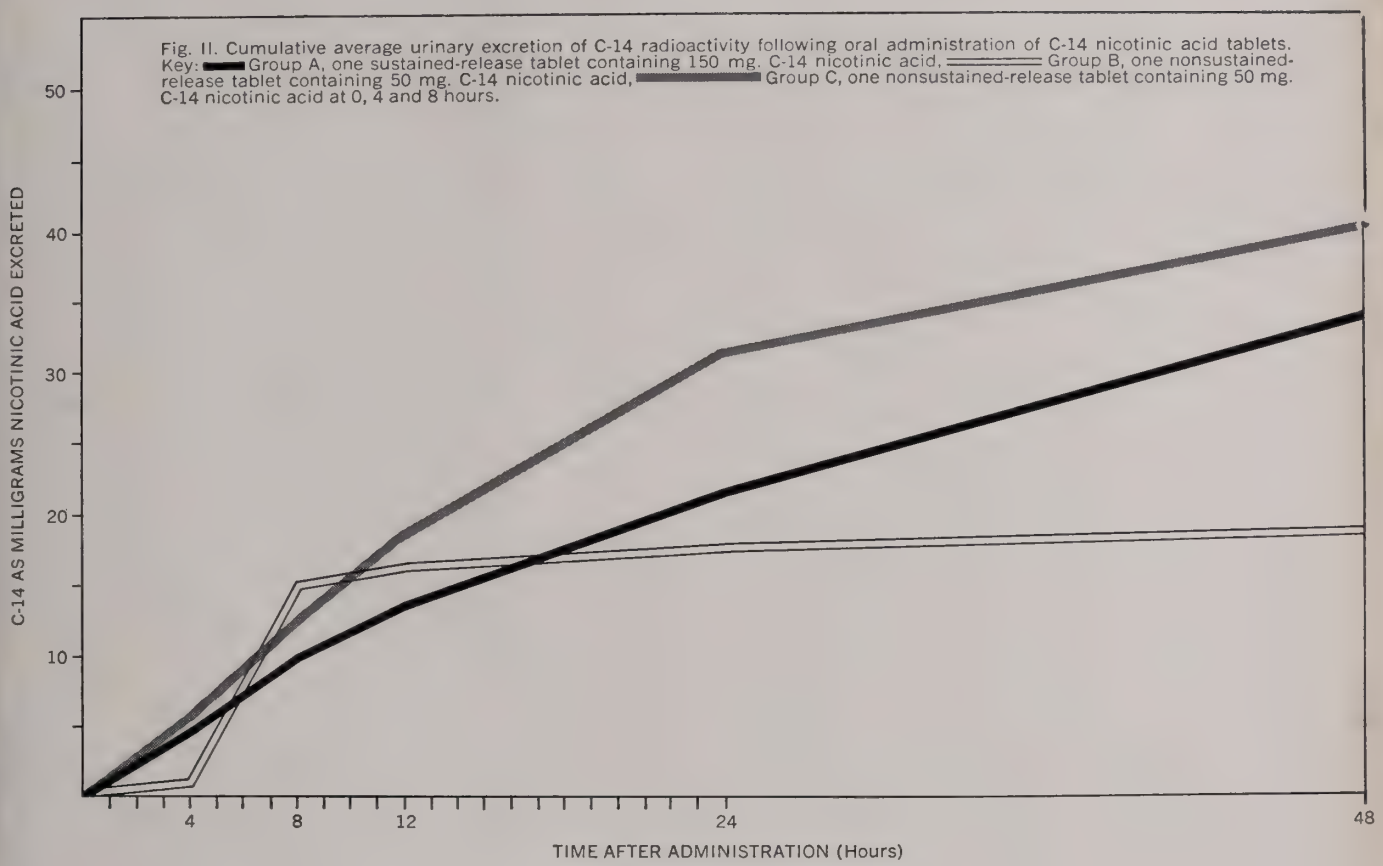
Human volunteer subjects were administered Geroniazol TT tablets with the nicotinic acid component made radioactive with C-14. Plasma and urine samples were analyzed. (See Figures I and II) The radioactive tracer study substantiated the previous clinical evidence that the release of nicotinic acid from the Geroniazol TT tablet produced a gradual rise in plasma levels to a plateau for a total of 12 hours and more.

Such proven sustained activity makes the management of geriatric patients much easier by minimizing the possibility of neglected doses through absent-mindedness or senile confusion. Therapy *can* be continuous on a daily dose of only one Geroniazol TT tablet every 12 hours.

The gradual release of nicotinic acid in Geroniazol TT will provide the well-known peripheral vasodilatation needed in patients with deficient circulation and with a minimum amount (if any) of "flushing." Also, cerebrovascular circulation is complemented by pentylenetetrazol, long-established as a cerebral and respiratory stimulant.

Geroniazol TT improves the typical, unfortunate, signs of senile confusion. Patients become more alert,

aged and debilitated



less confused and moody. Personal care, memory, emotional stability, social attention improve. Fatigue, apathy and irritability are reduced.

A prescription for 100 tablets of Geroniazol TT will permit your patients to enjoy the benefits of time-prolonged nicotinic acid/pentylenetetrazol therapy, at an economical price. Dosage is only one tablet every 12 hours.

Contraindications: There are no known contraindications.

Precautions: Exercise caution when treating patients with a low convulsive threshold.

Side Effects: Side effects are rarely encountered, however due to the vasodilatation effect of nicotinic acid, transitory mild nausea, flushing, tingling and pruritus are possible.

Dosage: One tablet every 12 hours.

Supplied: Prescribe bottles of 100 tablets, to take advantage of recent price reduction.

References: 1. Report by Nuclear Science & Engineering Corp., Pittsburgh, Pa., in files of Philips Roxane Laboratories. 2. Connolly, R.: W. Virginia Med. J. *56*:263 (Aug.) 1960. 3. Curran, T. R., and Phelps, D. K.: Am. Pract. & Digest Treat. *11*:617 (July) 1960.

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PHILIPS ROXANE LABORATORIES
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Geroniazol® TT

nicotinic acid 150 mg., pentylenetetrazol 300 mg.
Tempotrol® Time Controlled Tablet





Tissue's healing nicely. Yet anxiety slows his steps toward recovery.

By helping overcome anxiety and tension which can thwart the convalescent's progress, Equanil® often may play an important role in medical and surgical aftercare.

Indications: For use in management of anxiety and tension occurring alone or as accompanying symptom complex to medical and surgical disorders and procedures. Though not a hypnotic, fosters normal sleep through antianxiety and related muscle-relaxant properties.

Contraindications: History of sensitivity to meprobamate.

Important Precautions: Carefully supervise dose and amounts prescribed, especially for patients prone to overdose themselves. Excessive prolonged use has been reported to result in dependence or habituation in susceptible persons, as alcoholics, ex-addicts, and other severe psychoneurotics. After prolonged excessive dosage, reduce dosage gradually to avoid possibly severe withdrawal reactions. Abrupt discontinuance of excessive doses has sometimes resulted in epileptiform seizures.

Warn patients of possible reduced alcohol tolerance, with resultant slowing of reaction time and impairment of judgment and coordination.

Reduce dose if drowsiness, ataxia or visual disturbance occurs; if persistent, patients should not operate vehicles or dangerous machinery.

Side Effects include drowsiness, usually transient; if persistent and associated with ataxia, usually responds to dose reduction; occasionally concomitant CNS stimulants (amphetamine, mephentermine sulfate) are desirable. Allergic or idiosyncratic reactions are rare, but such reactions, sometimes severe, can develop in patients receiving only 1 to 4 doses who have had no previous contact with meprobamate. Previous history of allergy may or may not be related to incidence of reactions. Mild reactions are characterized by itchy urticarial or erythematous maculopapular rash, generalized or confined to groin. Acute nonthrombocytopenic purpura with cutaneous petechiae, ecchymoses, peripheral edema and fever have been reported. One fatal case of bullous dermatitis following intermittent use of meprobamate with prednisolone has been reported. If allergic reaction occurs, meprobamate should be stopped and not reinstituted. Severe reactions, observed very rarely, include angioneurotic edema, bronchial spasms, fever, fainting spells, hypotensive crises (1 fatal case), anaphylaxis, stomatitis and proctitis (1 case) and hyperthermia. Treat symptomatically as with epinephrine, antihistamine and possibly hydrocortisone. Aplastic anemia (1 fatal case), thrombocytopenic purpura, agranulocytosis and hemolytic anemia have occurred rarely, almost always in presence of known toxic agents. A few cases of leukopenia, usually transient, have been reported on continuous administration.

Meprobamate may sometimes precipitate grand mal attacks in patients susceptible to both grand and petit mal. Extremely large doses can produce rhythmic fast activity in the cortical pattern. Impairment of accommodation and visual acuity has been reported rarely. After excessive dosage for weeks or months, withdraw gradually (1 or 2 weeks) to avoid recurrence of pretreatment symptoms (insomnia, severe anxiety, anorexia). Abrupt discontinuance of excessive doses has sometimes resulted in vomiting, ataxia, tremors, muscle twitching and epileptiform seizures. Prescribe very cautiously and in small amounts for patients with suicidal tendencies. Suicidal attempts have resulted in coma, shock, vasomotor and respiratory collapse and anuria. Excessive doses have resulted in prompt sleep; reduction of blood pressure, pulse and respiratory rates to basal levels; and occasionally hyperventilation. Treat with immediate gastric lavage and appropriate symptomatic therapy. (CNS stimulants and pressor amines as indicated.) Doses above 2400 mg./day are not recommended.

Composition: Tablets, 200 mg. and 400 mg. meprobamate. Coated Tablets, WYSEALS® EQUANIL (meprobamate) 400 mg. (All tablets also available in REDIPAK® [strip pack], Wyeth.) Continuous-Release Capsules, EQUANIL L-A (meprobamate) 400 mg.

Wyeth Laboratories Philadelphia, Pa.

Wyeth® SERVICE TO MEDICINE

Equanil®

(meprobamate)

Wyeth

Professionally posed.



Classified

Classified advertising rates are twenty (20) cents a word; minimum monthly charge $5.00; key number, fifty (50) cents additional.

Replies to advertisements with key numbers should be mailed in care of Minnesota Medicine, 375 Jackson, St. Paul, Minn. 55101.

GENERAL SURGEON, Certified, part or full-time association in multi-specialty clinic. Alfred F. Anderegg, M.D., 645-5851, 2500 Como Ave., St. Paul, Minnesota.

WANTED: GP to join clinic serving population area of 12,000. City has new hospital, new clinic building, two nursing homes, new Jr-Sr high school, new swimming pool, rich farming area in Red River Valley. Fishing and hunting nearby; metropolitan city close by. Salary open and partnership if interested. Write or call Warren Clinic, Warren, Minnesota 742-6231, area code 218.

WANTED: General practitioner, to join two G.P.'s well established in north central Minnesota community, 2200 pop., 65 miles from Twin Cities. Excellent office space with lab and X-ray, just opened new hospital, all facilities. Assistantship or partnership. Considerable surgery and obstetrics. Hunting, fishing, golf club. Great opening for interested G.P. WRITE MINNESOTA MEDICINE—381; 375 Jackson, St. Paul, 55101.

INTERNIST AND GENERAL PRACTITIONER wanted to join a five-man clinic group in Minneapolis. Complete laboratory and X-ray with board roentgenologist. Excellent hospital staff associations. Salary arrangement to start with early partnership. Write: MINNESOTA MEDICINE—289; 375 Jackson, St. Paul, 55101.

SEVENTEEN-MAN Wisconsin group located in college community of 40,000 with excellent hospital facilities is seeking additional associates in the following areas: (1) Internal Medicine, (2) General Surgery and (3) General Practice. For further information please contact D. R. Griffith, M.D., Midelfart Clinic, Eau Claire, Wisconsin.

WANTED: GENERAL PRACTITIONERS, anesthesiologist, Urologist, Obstetrician, Orthopedist, & Pediatrician needed in growing community of 15,000. Service area 25,000. Present 83 bed general hospital. New 100+ bed automated hospital to be completed within 2 years. City has excellent industry, school system, and recreational activities. 45 minutes from Madison or Milwaukee. Future unusually promising. For more information contact: Administrator, Watertown Memorial Hospital, Watertown, Wis.

GENERAL PRACTITIONER with 25 years experience and a well-established practice in a suburb of the city desires a General Practitioner with an association towards a partnership. Write: MINNESOTA MEDICINE-389, 375 Jackson, St. Paul 55101.

Classified Advertisements

PHYSICIAN WANTED: G.P. with additional surgical and OB experience—desired to associate with two G.P.'s with similar experience in large, well established practice in Central Minnesota. Hospital accredited, 300 bed, open staff, complete services. Salary leading to partnership. Adequate housing in area. Send background information, professional and personal to: Dr. Goehrs, 825 First Street North, St. Cloud.

THREE MAN group in North West Wisconsin Resort, State Conservation and Retirement Area needs two more physicians adequately to serve their practice. Facilities offered are three-room physician suites, X-ray and lab under AMT technician, RN-only nursing personnel. New accredited thirty-two bed hospital and forty-six bed nursing home. Deer and duck hunting, fishing within five minutes of town. Internist most needed; generalists welcomed. Will meet any reasonable salary request. Partnership after one year. Write: MINNESOTA MEDICINE—365; 375 Jackson St., St. Paul 55101.

WANTED—YOUNG GP, to join 8-man group of 6 GP's, a general surgeon, and a radiologist; college town of 5500 only 30 miles from Twin Cities; salary negotiable with early partnership opportunity. Write or call collect: Ed Jenkins, Mgr., River Falls Medical Clinic, River Falls, Wisconsin. Phone 425-5322.

GENERAL PRACTITIONER wanted to join well-established practitioner. New clinic building—90 miles east of St. Paul—city of 14,000. Early partnership with full hospital facilities. Ideal location. L. W. Picotte, M.D.; Chippewa Falls, Wisconsin.

WANTED: YOUNG PHYSICIAN for association leading to partnership with four well-established General Practitioners in fast-growing suburb of St. Paul. Excellent clinic facilities in nearly new, partnership owned, well equipped, medical center building. Contact: A. Eugene Muller, M.D., North St. Paul Medical Center, 2579 East 7th Avenue, North St. Paul, Minnesota 55109.

GENERAL PRACTITIONER wanted to join well established practitioner in city of 5-6,000 and serving a population area of 18-20,000. Approximately 75 miles west of Mpls.-St. Paul. Well-kept clinic building two blocks from the hospital. Fully accredited 80 bed hospital with a resident Pathologist, Radiological Service, LPN School, X-ray Technician School, and complete Physiotherapy Department. Short-term association on salary basis or long-term association with eventual partnership, will accept, consider and appreciate either terms. Please send short resume of your education and previous experience. For further information about this opportunity write: Gregory M. Olson, M.D., Litchfield, Minnesota 55355.

WANTED—YOUNG INTERNIST. Board certified or eligible, to join 8-man group consisting of 6 GP's, a general surgeon, and a radiologist; college town of 5500 only 30 miles from Twin Cities; salary negotiable with early partnership opportunity. Write or call collect: Ed Jenkins, Mgr., River Falls Medical Clinic, River Falls, Wisconsin, phone 425-5322.

Continued

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- EMPHYSEMA
- ASTHMA
- CHRONIC BRONCHITIS
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Each tablet contains:

Potassium Iodide	195 mg.
Aminophylline	130 mg.
Phenobarbital, Caution: May be habit forming...	21 mg.
Ephedrine HCl	16 mg.

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DISPENSING WITHOUT PRESCRIPTION

Precautions: Usual for aminophylline-ephedrine-phenobarbital. Iodides may cause nausea, long use may cause goiter. Discontinue if symptoms of iodism develop.

Iodide contraindications: tuberculosis, pregnancy.

DOSAGE

One tablet, with full glass of water, 3 or 4 times daily.

Dispensed in bottles of 100 and 1000 tablets.

MUDRANE GG—Formula, dosage and package identical to Mudrane—*except*—100 mg. glyceryl guaiacolate replaces the potassium iodide. The value of Mudrane cannot be enjoyed by a small group in which K.I. is contraindicated. Mudrane GG is prepared for this group.

MUDRANE GG ELIXIR—Four 5 cc teaspoonfuls is equivalent to one Mudrane GG tablet. Dosage adjusted to age and weight of child. Mudrane GG Elixir is for pediatric patients and those who think they cannot swallow tablets. Dispensed in pint and half gallon bottles.

WM. P. POYTHRESS & CO., INC.
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Manufacturers of ethical pharmaceuticals since 1856

GENERAL PRACTITIONER OR INTERNIST needed in six man group in Northeastern Minnesota. 38 bed accredited hospital next door to modern clinic, rotating call schedule, over 4 wks. vacation per year, study and sick leave, group paid disability and retirement plans, and full partnership in 6 months. Starting guarantee $18,000 to $22,000 with increases to $26,000 to $28,000 over 4 years. Ideal opportunity for man desiring association with active group in small community offering good income plus ample time off. Contact Harold B. Leppink, M.D., Community Clinic, Two Harbors, Minnesota. Phone Area 218 834-2171.

GENERALIST as member of Medical Staff of progressive State Hospital in Michigan's vacationland. Hospital has 3-year accreditation, JCAH and 3-year residency accreditation by A.P.A. Salary $16,000 to $19,800. Excellent fringe benefits. Civil Service security when qualified. Apply L. B. Young, M.D., Director of Medical Services, Traverse City State Hospital, Traverse City, Michigan 49684.

DENTIST INTERESTED IN BUILDING MEDICAL BUILDING in Plymouth Village on Highway 55, west of Golden Valley. Rapidly growing community with no present M.D. in area. Anyone interested in partnership contact: Dr. James H. Hunder, 11335B Highway 55, Minneapolis 55427.

PHYSICIAN interested in internal medicine wanted for medical service. Starting salary $13,507 to $18,481, depending on qualifications. Liberal fringe benefits. An equal opportunity employer. Contact Chief of Staff, Veterans Administration Hospital, Des Moines, Iowa 50308.

MADDOCK needs a General Practitioner or preferably two, to take over a well-established practice. Present physician leaving for Philippines in the Spring. Progressive community, large area, modern 22-bed hospital, separate clinic, new school under construction. If financial independence, a real desire to help our people and becoming one of us interests you, contact Donna Rice, Memorial Hospital, Maddock, North Dakota.

FOR SALE: Modern clinic building 44 x 80, brick and block construction. Seven years old, adequate examination, emergency treatment and X-ray rooms, plus private offices, and laboratory rooms. Fully air-conditioned. Located in West Central Minnesota, City of Approximately 5000 population. Write: MINNESOTA MEDICINE-392, 375 Jackson St., St. Paul 55101.

PEDIATRICIAN—to join established department of pediatrics in 17-man mid-western group. Excellent opportunity in a growing-dynamic clinic with early partnership. Town of 33,000 with two hospitals and excellent schools. Clinic staff enjoys regular vacations and time off for study. Write: MINNESOTA MEDICINE-393, 375 Jackson St., St. Paul 55101

WANTED: LOCUM TENENS for general practice for July or August, 1968. Salary open. Location within one hour's driving from Twin Cities. Write: MINNESOTA MEDICINE-395, 375 Jackson St., St. Paul 55101.

OPENING IN MT. LAKE, Minnesota for General Practice. Associate practice if desired, adequate vacations, excellent office space, financial help if needed, new 25-bed hospital, nursing home, two old people's homes, over 100-bed capacity in total. Excellent schools and churches. If interested, call collect 427-3515 Mt. Lake, Minnesota or contact Steinle Drug.

BUSY THREE-MAN general practice group desires another physician. Excellent salary and early partnership consideration. On call one night during the week and every fourth weekend. Town of 5,000, located 150 miles northeast of Minneapolis. 50 bed hospital. Superior educational and recreational facilities. Call 631-1360 collect or write Davis Clinic, 22 Dayton Avenue Southeast, Wadena, Minnesota 56482.

FOR RENT: Doctors attractive air-conditioned office; one story brick building. Unit has lab, x-ray, office, pleasant reception room and four examining rooms. Parking no problem. Dodd & Morton, St. Paul West Side. Telephone 224-2366 or 226-1189.

DESIRE LOCUM TENENS in General Practice. Minnesota graduate. Available July thru December 1968. Mark A. Mathison, M.D., 6060 Munson Hill Road, Falls Church, Virginia 22044.

OPHTHALMOLOGIST AND PEDIATRICIAN needed by an established seven man group in an attractive situation one hour from Twin Cities. Excellent facilities in a community of 12,000 with drawing to 50,000. Wholesome atmosphere for raising a family. First year salary open, partnership after one year. Write H. J. Williams, M.D., Medical Block Clinic, Red Wing, Minn. 55066, or phone 612-388-4751.

RESIDENCIES IN PHYSICAL MEDICINE and Rehabilitation offer challenge and opportunity in a growing field. Comprehensive training utilizing Mayo Clinic facilities and faculty, at $5,400 to $10,000 stipend. Attractive community, excellent school system, cultural advantages. Contact Gordon M. Martin, M.D., Mayo Graduate School of Medicine, Rochester, Minnesota 55901.

NEWBERRY STATE HOSPITAL—Tired of the urban rat race? Bumper-to-bumper expressways? Polluted air? Working inhuman hours? Living next to your neighbors for years and never getting to know them? Change your way of life to what it should be and still continue to practice your profession at an attractive rate of compensation. The Newberry State Hospital, located in the heart of Michigan's vacation land, has a number of opportunities for both psychiatrists and general practitioners. Salaries up to $25,265* depending upon qualifications. Eligibility for Michigan license required. Excellent retirement program, insurance plans, sick and annual leave, and other fringe benefits provided by Michigan Civil Service. For more details write, wire, or call collect William R. Purmort, M.D., Medical Superintendent, Newberry State Hospital, Newberry, Michigan 49868. (*Pending legislative approval, anticipated salary as of July 1, 1968.) An Equal Opportunity Employer.

FOR SALE, new equipped clinic, unopposed general practice established twelve years; dentist in clinic; new hospital in town; Lake Mille Lacs Area. Write MINNESOTA MEDICINE-396, 375 Jackson St., St. Paul 55101.

Continued on page 592



NORTHLANDS REGIONAL MEDICAL PROGRAM

REGIONAL PROGRAM FOR HEART DISEASE, CANCER AND STROKE

Last month this feature defined Regional Medical Programs and described the origin of the Minnesota Program. The question and answer format will be continued to describe the program.

What is a Region?

There are 54 Regional Medical Programs in the country. They vary geographically from a small part of one state (Metropolitan New York) to parts of five states (Intermountain Region centered on Salt Lake City, Utah). Most Upper Midwest Regions follow state lines (Iowa, Wisconsin, Minnesota, North Dakota). Nebraska and South Dakota joined to form one region.

What are the Medical Centers of Regional Medical Programs?

A medical center is defined as "a medical school or other medical institution involved in post-graduate medical training and one or more hospitals affiliated therewith for teaching, research and demonstration purposes."

In Minnesota the University of Minnesota College of Medical Sciences and the Mayo Foundation are the medical centers.

Where are the Central Offices of Northlands Regional Medical Program?

Northlands Regional Medical Program offices are located in the new quarters of the Minnesota State Medical Association on the fifth floor of the new Farm Credit Banks Building at 375 Jackson Street in Saint Paul, Minnesota

How does Northlands Regional Medical Program Operate?

Authority rests with an Executive Committee consisting of one representative from each of the nine sponsoring organizations. The Program Coordinator, Chairman of the Executive Committee, and representative of the Minnesota State Medical Association, is Dr. J. Minott Stickney. Other members of the committee with the organizations they represent are: Jack Rivall, M.H.A., Minnesota Hospital Association; Robert A. Ulstrom, M.D., University of Minnesota College of Medical Sciences; Jack P. Whisnant, M.D., Mayo Foundation; Robert N. Barr, M.D., Minnesota Board of Health; William F. Mazzitello, M.D., Minnesota Heart Association; Donald E. Stewart, M.D., Minnesota Cancer Society; Paul M. Ellwood, M.D., American Rehabilitation Foundation; and Harold W. Brunn, L.L.B., Minnesota State Medical Association Foundation.

A Regional Advisory Group composed of lay and professional representatives of health related organizations is required by law to appraise and approve all operational programs.

Who are Employed by Northlands Regional Medical Program?

The following personnel are employed full-time in the Central Office: Winston R. Miller, M.D., Program Director; Robert J. Wilkins, M.H.A., Associate Director; Ivan J. Fahs, Ph.D., Medical Sociologist; and Lawrence B. Stadler, M.P.H., Coordinator for Heart Disease Programs. Unfilled positions call for a Biostatistician and Research Associates or Coordinators.

The following personnel are employed at the Medical Centers (all but one are part-time): Mayo Clinic: J. Minott Stickney, M.D. and Jack P. Whisnant, M.D.; University of Minnesota College of Medical Sciences: Robert A. Ulstrom, M.D.; W. Albert Sullivan, M.D.; and Lee D. Stauffer, M.P.H. (full-time).

The program also pays for time and expenses of laymen and physicians from throughout the state who serve on working committees.

Can Federal Subsidies Weaken the "Town-Gown" Syndrome and Other Bigoted Barriers to Facilitate More Effective Delivery of Health Care Services?

This is the crucial question. In Minnesota, as in 53 other "regions," we are given the chance to try.

Winston R. Miller, M.D., F.A.C.P.
Program Director

Keep the World in Balance

The child who has watched the miracles of new plants breaking through the earth in the spring; who has kept a silent vigil in observing a robin's nest; who has studied the stars and pondered the mysteries thereof; who has walked with Nature and talked with God, and stood in awe of the universe . . . has learned more than he'll ever learn from books. If he can retain his interest in the world, during those trying years of being polished on the grindstone . . . if he can look up to the heavens and down to the earth and keep his world in balance . . . he will surely be among the nineteen-out-of-twenty who will never spend time in a mental hospital.*

*James Fisher, M.D.: A Few Buttons Missing, 1951.

Preventive Medicine Seminar

A Preventive Medical Seminar will be held at St. Luke's Hospital, St. Paul, on Thursday, April 25th. The seminar will start with a general staff buffet luncheon at 12:30 and end with a 5:00 p.m. social hour. Contact: K. M. Lawler, M.D., Chairman, St. Luke's Hospital, St. Paul.

Speeches

Speeches are like babies—easy to conceive but hard to deliver.—Anon.

Constitutional Statesmen

Constitutional statesmen are obliged, not only to employ arguments which they do not think conclusive, but likewise to defend opinions which they do not believe to be true.—Bagehot



Meetings and Announcements

A skeptic is not one who doubts, but one who examines.—Sainte-Beuve

APRIL

Nicollet-LeSueur County Medical Society Meeting, April 1, Holiday House. Dr. Werner Simon speaking, 6:30 P.M.

Southwestern Minnesota Medical Society, April 1, Ehlers Supper Club, 7:00 P.M.

Goodhue County Medical Society, April 2, St. James Hotel, 6:30 P.M.

Scott-Carver County Medical Society, April 2, Wagner Supper Club, Jordan, 7:30 P.M.

Minnesota Academy of Ophthalmology & Otolaryngology, April 5, Minneapolis Club, 6:30 P.M.

Minnesota Academy of Medicine, April 10, Town and Country Club, St. Paul, 7:00 P.M.

Camp Release District Medical Society, April 11, Monthly Meeting, Hunt Hotel, Montevideo, 7:30 P.M.

St. Louis County Medical Society, April 11, Executive Committee, St. Luke's Hospital, 6:00 P.M.—Regular Meeting, St. Luke's Hospital, 8:00 P.M.

Minnesota Academy of General Practice, House of Delegates, Hotel Radisson, 1:00 P.M., April 16; Annual Refresher, Hotel Radisson, 8:00 A.M.-5:00 P.M., April 16-18.

Blue Earth Valley Medical Society, April 17, Regular Meeting, Interlaken Golf Club, Fairmont, 7:00 P.M.

Kandiyohi-Swift-Meeker County Medical Society, April 18, Westwood Inn, Spicer, 7:00 P.M.

McLeod County Medical Society, April 18.

Twin City Urological Society, Town and Country Club, St. Paul, 6:30 P.M., April 19.

Blue Earth County Medical Society, April 22, Century Club, 8:00 P.M.

Minnesota Obstetric and Gynecological Society, April 27, Mayo Clinic, Rochester, 9:00 A.M.

Upper Mississippi Medical Society, Spring Meeting, St. Gabriel's Hospital, Little Falls, 2:30 P.M., April 27.

Ramsey County Medical Society, April 29, Regular Meeting, 1500 Lowry Medical Arts Building, 8:00 P.M.

The Minnesota Thoracic Society and the Minnesota Respiratory Health Association announce a second award contest for medical students, interns and resident physicians in Minnesota.

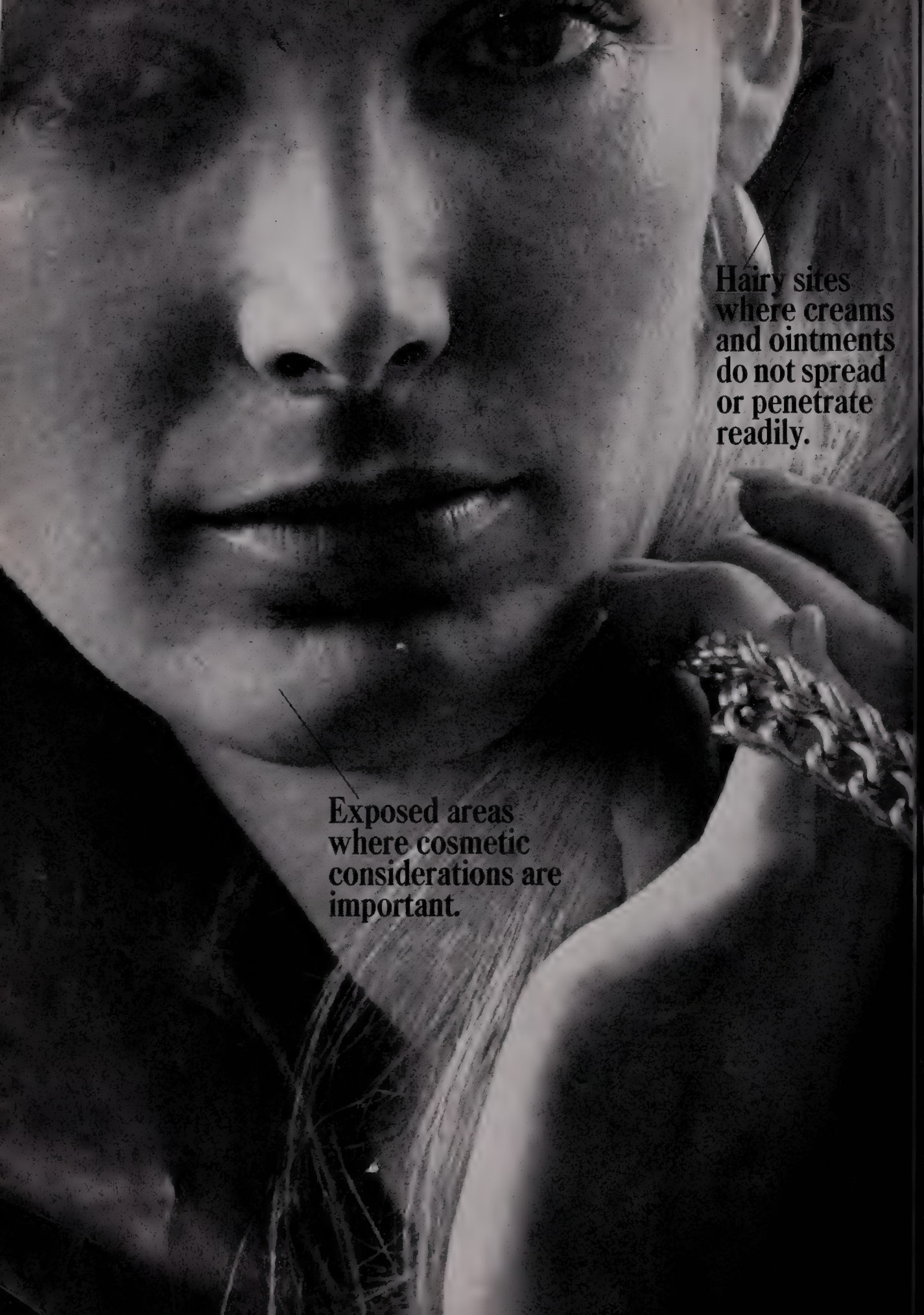
(A) An award of $200.00 is offered for the best paper submitted by a senior medical student or intern on some aspect of respiratory disease, preferably based upon laboratory or clinical investigation.

(B) An award of $300.00 is offered for the best paper submitted by a resident physician based upon clinical or laboratory investigation in the area of respiratory disease.

Further information may be obtained from the Secretary. Entries should be submitted by September 1, 1968 to: David E. Dines, M.D., Secretary, Minnesota Thoracic Society, Mayo Clinic, Rochester, Minnesota.

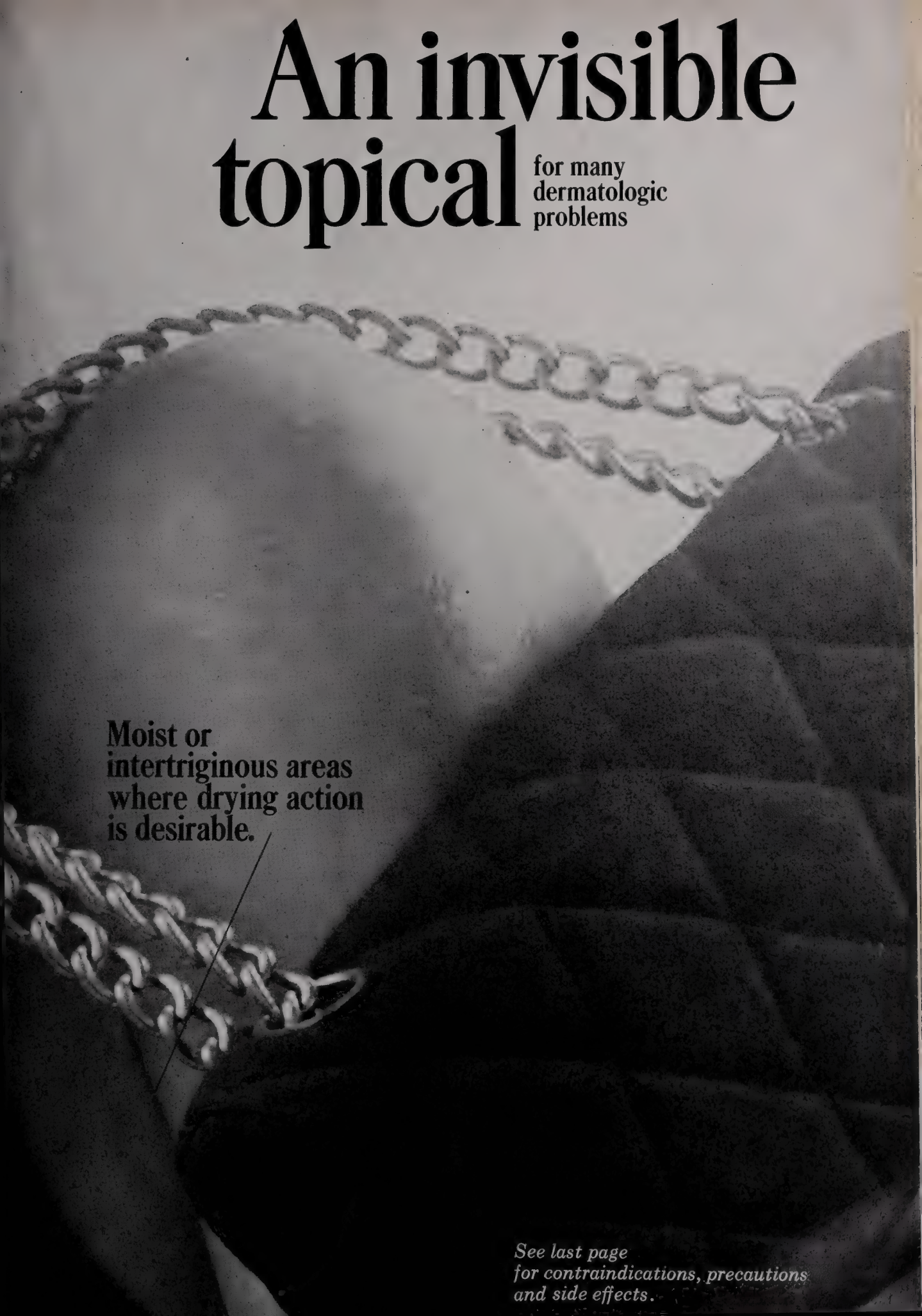
L. E. Phillips Psychobiological Research Divisions of North Memorial and Mount Sinai Hospitals with The Minnesota Heart Association Symposium on Heart and Emotions. North Memorial Hospital auditorium, April 7, 1968. Afternoon and evening sessions (1:15 p.m. to 8:45 p.m.), with dinner being served at 5:30 in the hospital dining room. Attendance has been approved by the Academy of General Practice for 6 hours of Post-Graduate Study. Since the number of registrants will be limited, they will be accepted by acknowledgment in the order received. Contact Ralph Rossen, M.D., 588-0616, extension 301, or 339-1692, extension 596.

The Minnesota Symposium on Prevention in Cardiology. Reducing the Risk of Coronary and Hypertensive Disease. May 2nd and 3rd, 1968, Mayo Clinic, Rochester, Minnesota. Sponsored by: The Minnesota Heart Association, The Mayo Foundation and The University of Minnesota. Information available from: Henry Blackburn, M.D., Stadium Gate 27, University of Minnesota, Minneapolis, Minnesota 55455.


Hairy sites where creams and ointments do not spread or penetrate readily.
Exposed areas where cosmetic considerations are important.

An invisible topical

for many dermatologic problems



Moist or intertriginous areas where drying action is desirable.

See last page for contraindications, precautions and side effects.

Structurally unique topical steroid in propylene glycol vehicle produces rapid response in many dermatoses.

Synalar Solution produces rapid antiinflammatory, antipruritic action through its unique topical corticosteroid, fluocinolone acetonide. The propylene glycol vehicle provides additional benefits for therapy at problem sites where it is difficult to achieve contact between the lesion and medication – or where creams or ointments may make the lesions worse. Synalar Solution has proved particularly valuable in the symptomatic treatment of seborrheic dermatitis of the scalp, nasolabial folds, eyebrows, ears, and in flexural folds such as the axillae, inframammary, umbilical and anocrural areas. It has also been reported to achieve excellent results in the adjunctive management of atopic dermatitis, contact dermatitis, neurodermatitis, nummular eczema, psoriasis, and sweat retention syndromes in these problem sites.

Penetrates the hairy sites.

In many areas of the body, hair gets in the way of treating the underlying dermatitis. The propylene glycol vehicle of Synalar Solution permits penetration and dispersion at sites where creams and ointments do not readily penetrate. May be applied without matting of hair.

Ideal for moist or intertriginous areas.

Propylene glycol is strongly hygroscopic and is especially useful where sweat retention is a problem. Its low surface tension permits easy spreadability in difficult-to-treat body areas. A number of studies have also shown that propylene glycol has inherent antimicrobial activity.



Cosmetically acceptable for exposed areas.

The propylene glycol vehicle of Synalar Solution possesses many useful cosmetic properties. Clear and greaseless, it is not sticky or messy, will not stain clothing or skin. In exposed areas of the body where cosmetic appeal is important, Synalar Solution shows nothing but results.

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(Continued from page 584)

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What's New

Wyeth supplies first coral-snake antivenin! The first U. S. licensed and produced Antivenin to combat the North American eastern coral snake has been developed by Wyeth Laboratories and is now available in the nine states where coral snakes are found. The company has donated the Antivenin to the health centers in the nine states of Georgia, Florida, Alabama, Arkansas, Louisiana, Mississippi, North Carolina, South Carolina and Texas. Requests for Antivenin outside this nine state area must be referred directly to the National Communicable Disease Center, Atlanta, Georgia. Wyeth also produces the only licensed Antivenin for the poisons from pit vipers, rattlesnakes, copperhead and cottonmouth moccasins.

Loridine (cephaloridine), a new broad-spectrum antibiotic, is being introduced by Eli Lilly Company for the treatment of serious infection, including streptococci, staphylococci, hemophilus and colon organisma. It is recommended that the antibiotic not be used until the results of culture and sensitivity tests have been obtained and the renal function of the patient has been demonstrated to be adequate. Dosage in the excess of four grams daily has been associated with nephrotoxicity. Loridine is similar to Keflin, but intramuscular injection with Loridine is virtually free of pain.

Attendance

He has been a doctor a year now and has had two patients—no, three, I think—yes, it was three; I attended their funerals.—*Mark Twain*

Minnesota Medicine at a Glance

Atherosclerotic Cardiovascular Disease—Buchwald et al. Page 477

A rare and interesting case of true homozygous hypercholesterolemia is reported. Since the relationship of cholesterol and atherosclerosis is currently receiving a great deal of study and discussion, the implications of such a case are truly fascinating. The authors report the devastating effects of advanced atherosclerosis in a 14-year-old boy with this unique congenital disturbance, and of their attempt to ameliorate the problem. This case has served as a small, well defined, clinical experiment in the solution of the overall problem of atherosclerosis.

Precancer and Cancer of the Skin—Peterson Page 483

The chief difficulty concerns excess words and some difficult sentence structures. A number of word and sentence changes have been suggested. With these changes the paper is considered acceptable. There are six figures, but the photographs for the figures were not included with the paper submitted for review. The figures should be examined for quality.

The following is a summary: "There are a number of dermatological conditions which are considered to be precancerous. The differential between benign and malignant conditions is difficult in such skin problems as actinic keratosis, leukoplakia, arsenical keratosis, radiodermatitis, and pigmented nevi. The management of these difficult problems in skin disease is presented."

Incarceration of Transvenous Pacemaker Electrode—Bilgutay et al. Page 489

Temporary or permanent myocardial pacing by an intravenous electrode is a recognized therapeutic measure for multiple cardiac arrhythmias. Although removal of the pacemaker wire from the heart is usually not a problem, the authors describe two patients in whom removal was a problem. A simple technique of gentle traction by a one-half to two-pound weight proved effective. A successful removal may have saved the patients from a thoracotomy and cardiotomy or other complications of a retained electrode.

Errata

Abdominal Mass and Acute Leukemia—Clinical Path Conference. 51 :260, 1968.

Reference is made to two new drugs in the treatment of leukemia in my discussion. In referring to Daunomycin the text would suggest that Daunomycin is the same as L-Asparaginase, and these are of course two entirely different compounds. Apparently an oversight on my correction of the text led to their being made to seem synonymous, which they are not.

Robert A. Green, M.D.
Minneapolis, Minnesota

Porphyria 51 :49, 1968.

We neglected to correct the word "synthesis" fourth line up, left hand column, in the above editorial. It should be "synthetase."

Harold O. Perry, M.D.
Rochester, Minnesota

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Kurt Schnitzer, M.D.

MAY, 1968

115th Annual Meeting Issue
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Precautions: Some individuals may experience drowsiness, anorexia, and slight gastric distress. If excessive drowsiness occurs, it may be necessary to increase the interval between doses. Persons on full dosage should not operate any vehicle. Use may result in overgrowth of nonsusceptible organisms. If infections appear during therapy, appropriate measures should be taken. Infections caused by beta-hemolytic streptococci should be treated for at least 10 full days to help prevent rheumatic fever or acute glomerulonephritis. Use of tetracycline during tooth development may cause discoloration of teeth.
Adverse Reactions: Gastrointestinal—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin—maculopapular and erythematous rashes (a case of exfoliative dermatitis has been reported); photosensitivity; onycholysis and discoloration of nails (rare). Kidney—rise in BUN, apparently dose related. Hypersensitivity reactions—urticaria, angioneurotic edema, anaphylaxis. In young infants, bulging fontanels following full therapeutic dosage has been reported. This has disappeared rapidly when drug was discontinued. Teeth—dental staining (yellow-brown) in children of mothers given tetracycline during the latter half of pregnancy and in children given the drug during the neonatal period, infancy, and early childhood. Enamel hypoplasia has been seen in a few children. Blood—anemia, thrombocytopenic purpura, neutropenia, eosinophilia. Liver—cholestasis (rare), usually at high dosage. If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy.

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327-8

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J. Minott Stickney, M.D.

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See the President's Letter, Page 601.



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President's Letter

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Dr. O. L. N. Nelson has kindly given me, as a past President, the opportunity to invite the members of the Minnesota State Medical Association to attend the Annual Meeting in Rochester during May 12 to 15.

In addition to the usual stimulating program which has been arranged for the entire meeting, there will be an interesting innovation at the annual banquet. Those of us who have had the honor of serving as your President have been impressed, when visiting our neighboring state associations, by the ceremony of induction of the Presidents.

In Minnesota, the incoming President quietly assumes office at midnight on New Year's Eve without any fanfare except that which may have been provided by his personal friends. This year, for the first time, our President will be honored by the presentation of a gold medallion which he may wear during his term of office.

A replica of the medallion in a bronze plaque will be awarded at the banquet to each of the 20 living past Presidents. We hope that all of them will be able to join you in this happy occasion on May 14.

J. M. Stickney, M.D.
Past President and Delegate
to the American Medical Association

In all this advance of science there is one grand, outstanding exception—the healing arts. All that cures or banishes disease, all that quenches human pain, and mitigates bodily infirmity, is welcome whatever view you take of religion, philosophy, or politics.—Winston Churchill, 1951

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STATE MEDICAL ASSOCIATION

minnesota medicine

Volume 51

Number 5

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A Bronchodilator Solution

Postoperative Use

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DURING RECOVERY from anesthesia, the surgical patient requires intensive care. The residual effects of anesthesia must be ablated in order that the patient regain his productive cough, re-establish his respiratory drive to the normal rate and thus assure that hypoxia or hypercarbia is corrected. An early return of normal ventilation reduces the incidence of atelectasis and other systemic complications. These efforts directed towards improving ventilation in the immediate post-surgical period should not, however, cause an increase in patient excitation with subsequent increased metabolic needs; for then the net result might be a decrease in blood and tissue oxygen tension.

We have for sometime used a bronchodilator solution, Bronkosol®†,[1-5] in the pre- and post-operative period to aid the patient to more rapidly recover normal ventilation. The use of this agent appeared to improve tolerance to intubation. Approximately 25,000 doses of the drug had been used for all age groups and all types of surgical patients. With few exceptions, our patients are intubated under demerol, pentothal, galamine and nitrous oxide anesthesia. The nitrous oxide and demerol are used as the major anesthesic agents.[6]

Objectives of Study

In order to check our clinical impressions of the effectiveness of the bronchodilator solution, studies were designed to give information on the effect of Bronkosol inhalations on the surgical patient in the immediate postoperative period. We were primarily interested in its effect on respiratory rate, minute volume, pulse rate and blood pressure. In addition, we checked first, whether the type of surgery performed had any significant effect on these measurements; and second, what the effects of Bronkosol were in patients with hyperten-

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†Bronkosol® contains: Dilabron® (brand of isoetharine) methanesulfonate HCL 1.0%, phenylephrine HCL 0.25% and thenyldiamine HCL 0.10%. Supplied by Breon Labs. Inc.

sion. Drug-related systemic effects were recorded, if observed.

Material and Methods

One hundred forty-nine patients were chosen from the general surgery schedule. Criteria for inclusion were: (1) major surgery, (2) reduced minute respiratory volume, (3) depressed respiratory rate, (4) symptoms or laboratory findings of respiratory acidosis, or (5) any combination of these. Patients selected were classified according to the following surgical procedures:

	Procedure	Patients
I	Head and Neck	16
II	Chest	7
III	Right Upper Quadrant	21
IV	Left Upper Quadrant	41
V	Right Lower Quadrant	21
VI	Left Lower Quadrant	15
VII	Genitourinary	26
VIII	Leg and Hip Surgery	2

A dosage of 20 "squeezes" from a De Vilbiss #40 nebulizer was used for patients under 18 years of age and 30 inhalations for patients over 18. Trials, by the personnel administering the solution, indicated that approximately 4 drops (.26 ml.) of Bronkosol solution was nebulized with 20 squeezes and 6 drops (.40 ml.) with 30.

Control readings were made of the pulse rate and blood pressure immediately before administration of Bronkosol and then at 15-minute intervals for one hour. The "greatest change" in either direction was chosen as the maximum effect and was recorded. For instance, if fluctuations in blood pressure included a reduction of 10 mm/Hg. from control, followed by an increase of 15 mm/Hg. above control, only the 15 mm/Hg. figure would be recorded as the major effect.

Results

Table 1 presents the distribution of patients by initial pulse, blood pressure and amount of change in blood pressure.

Pulse Rate

Pulse rate changes less than 10 beats per minute from control occurred in 107 of the 149 patients; the rate increased more than 10 beats per minute in 21 patients and de-

TABLE 1

Distribution of Patients by Initial Pulse and Blood Pressure and by Change after Bronkosol

	Initial Pulse		Initial Systolic		Initial Diastolic	
Change	<95	>95	<140 mm/Hg	>140 mm/Hg	<90 mm/Hg	>90 mm/Hg
>+10	11	10	26	10	10	7
+10 to −10	63	44	36	35	51	57
>−10	4	17	12	30	5	19
Total	78	71	74	75	66	83

TABLE 2

Summary of Bronkosol Effects on Pulse and Blood Pressure

		Number of Patients	Initial Mean	Changed Mean	t	p Value
	150 mm/Hg and over	53	171.2±5.8	161.6±6.5	2.20	<0.05
Systolic	140-150	75	1.62.6±5.1	154.9±5.5	2.06	<0.05
	less than 140	74	119.9±2.4	124.6±3.9	2.20	<0.05
	over 90 mm/Hg	53	105.8±2 5	99.8±3.8	2.62	<0.02
Diastolic	90	30	90 ±0.0	89 3±4.0	0.35	....
	under 90	66	76.5±1.5	77.1±2.7	0.38	....
	Pulse					
	over 95	71	109.6±3.1	106.5±3.3	1.37	....
	95 or less	78	84.2±1.9	85.3±2.7	1.36	....

The calculated value determines the p value. The p value is the level of significance of the difference between the means.

creased more than 10 beats per minute in 21 patients.

Blood Pressure

Inhalation of Bronkosol produced only a moderate effect on the systolic blood pressures (mean pre-treatment systolic pressure 140 mm/Hg.). As indicated in Table 1, only 17 patients had an increase or decrease greater than 20 mm/Hg. from control. Diastolic pressures changed less than 10 mm/Hg. from control in 108 of the 149 patients.

A summary of the effect of Bronkosol on pulse and blood pressure is presented in Table 2, along with levels of significance. Note that the lower initial values tended to increase and the higher initial values tended to decrease.

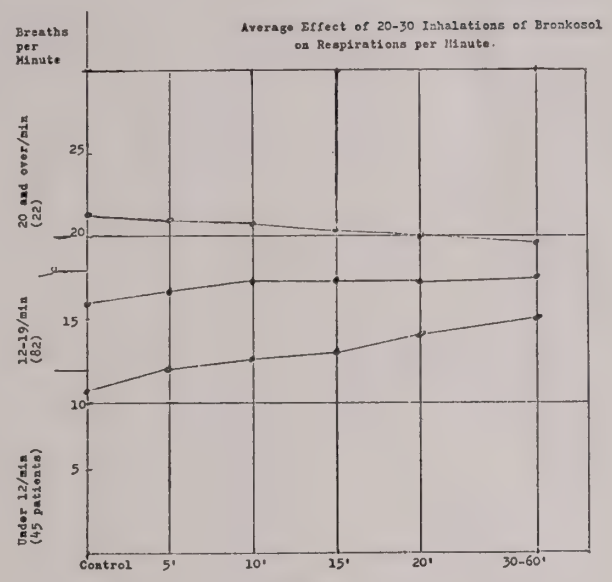
Respiratory Rate

The effect of Bronkosol on respiratory rate is presented in the illustration (Figure).

Note that the respiratory rate tended to decrease steadily in those patients with a control rate of more than 20. In contrast, the respiratory rate in patients with control values between seven and 12 breaths per minute increased noticeably. There was no significant effect on the group with control readings between 13 and 19 breaths per minute. The type of surgery was not significantly correlated with the respiratory rate in this series.

Respiratory Volume

Respiratory volume was measured using the Wright Expiratory Flowmeter. One-minute samples were measured at control, then at 5′, 10′, 15′, 20′ and 30-60′ after inhalation of



Figure

Bronkosol. (Twenty-four of the original 149 patients were eliminated from tabulations of minute volumes because of insufficient data or changes unrelated to Bronkosol therapy.)

The effect of ventilation of 20 or 30 breaths of nebulized Bronkosol on minute volume is presented in Table 3.

A significant increase was noted in those patients with depressed pre-treatment minute volumes. No significant difference was found between the groups treated with 20 as compared with 30 inhalations, although the difference tended towards significance in increased minute volume for the patients treated with 30 inhalations.

Control Group

In order to compare the results outlined

TABLE 3
Average Effect of Bronkosol on Minute Volume

Initial Minute Volume	Pre		5′	10′	15′	20′	30-60′	Number of Patients
0-3999 ml	20	3234	3693	4267	4500	5049		25
	30	3122	3612	4134	4272	4675	5086	15
4000-5999	20	4817	5182	5568	5958	6293		17
	30	4757	5043	5243	5758	6191	6326	8
6000-8999	20	6344	6843	7499	8173	8437		5
	30	6397	6433	6548	7318	7278	7263	3
9000 & over	20	14030	14350	14820	14810	14800		1
	30	....	....	....	....	....		0
All	20	4343	4770	5284	5614	6046		48
	30	4003	4378	4754	5081	5442	5719	26

previously with those of untreated patients, 30 similar post-surgical patients were chosen and the same measurements recorded. Except for elimination of the Bronkosol inhalations, the care of the patient remained the same.

Table 4 presents the summary of measurements of pulse rates and blood pressures in the control group.

Table 5 presents the summary of respirations per minute for the control group.

Table 6 presents the changes in respiratory minute volume for the control group.

Discussion

The anesthetized patient, whose respiration is being controlled, loses the natural reflexes of cough, sigh, and respiratory stimulation. In addition, inhalation of dry anesthetic gases causes chemical and physical irritation of the airway. As a result, the airway may be obstructed by dehydrated secretions, patches of atelectasis caused by absorption of oxygen or anesthetic gases behind the mucous obstructions, bronchial spasm and decrease in elastic compliance. In addition to these pulmonary complications, residual amounts of circulating sedatives and relaxants and the physical restriction of dressings tend to limit depth and frequency of respiration. Any technique which aids elimination of the anesthesia-related complications and restoration of normal respiratory reflexes and function hastens the postoperative recovery of the patients. Inhalation of Bronkosol, adequate replacement of fluid loss, and humidification of the inspired air are helpful and easily administrated.

It is our impression that these patients recovered more rapidly from their anesthetic state when the bronchodilator was used in the

TABLE 4

Results of Observation of Pulse and Blood Pressure in 30 Unmedicated Control Patients

Initial Pressure	Number of Patients	Systolic Pressure Initial	Systolic Pressure Change	Diastolic Pressure Initial	Diastolic Pressure Change	Pulse Initial	Pulse Change
150/90 mm/Hg and over	10	171.7±12.2	−3.8±12.1	103.8±5.4	−6.0±8.4	96.5±8.4	+2.3±6.2
Under 150/90	20	128.4± 3.2	+1 3± 8.0	80.1±4.5	+0.6±5.7	95 2±8.0	+3.8±6.6
All	30	142.8±10.1	−0.4± 6.6	88.0±5.4	−1.6±4.9	95.6±6.1	+3.3±4.8

TABLE 5

Average Respirations Per Minute in 30 Control Patients

Record Complete	0	5′	10′	15-20′	30-60′	Number of Patients
5 min	16.0	17.3				30
10 min	16.0	17.3	17.8			28
20 min	15.7	17.1	17.5	17 5		26
20-30 min	16.0	17.1	17.4	16.9	18.2	20

TABLE 6

Average Minute Volumes in 30 Control Patients

Initial Volume	0	5'	10'	15 20'	30-60'	Number of Patients
0.3999 cc (6 patients)	3420	3978	4116	4400	4925	6
	4995	5293				19
4000-5999	4800	5278	5501	5910		18
(19 patients)	4958	5221	5360	5641	5946	14
	7438	7719				5
6000-8000	7793	8149	9641			4
(5 patients)	7663	7682	7975	8195	9200	3

immediate postoperative period. Their respirations were stronger and more regular and title volume increased. While further studies are under way to measure the effects of bronchodilator therapy on compliance and perfusion, we believe that airway resistance is reduced and oxygenation improved.

Tolerance to Bronkosol therapy has been good with only moderate and usually beneficial effects on pulse and blood pressure. There appears to be no contraindication to the use of this agent in the patient with hypertension. This therapy has been used in patients with pre-existing cardiac conditions. Selected patients were monitored via cardioscope before and after the administration of Bronkosol. There has been no evidence, to date, of adverse cardiac effect.

We would encourage further study of the pre- and post-surgical use of bronchodilator and positive pressure therapy. Techniques which improve respiratory efficiency pre-surgically and help to restore normal pulmonary function in the postoperative period should be investigated and, if found successful, regularly employed.

Summary

One hundred forty-nine patients were treated in the postoperative recovery room with 20-30 inhalations of Bronkosol with the aim of increasing respiratory rate and depth as well as speeding recovery from the effects of anesthesia. The results of this therapy were measured at fixed intervals for one hour. Respiratory rate and minute volume tended to increase in the low and low-normal group. Pulse and blood pressure were not significantly affected. There was no evidence that the type of surgery performed significantly affected the post-surgical control recordings of pulse, blood pressure, respiratory rate or volume.

The administration of this bronchodilator solution during the post-surgical recovery period is well tolerated and appears to be useful in speeding recovery from anesthesia.

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Jackson's Syndrome

This syndrome is characterized by unilateral involvement of the last three cranial nerves: the vagus, spinal accessory, and hypoglossal. Their involvement may be recognized from the combined symptomatology consisting of ipsilateral paralysis of half of the soft palate and larynx, paralysis of the sternocleidomastoid and trapezius muscles, and hemiatrophy of the tongue. Jackson described this syndrome in 1864. Although usually caused by an intracranial lesion, it may sometimes arise in one lateral half of the medulla oblongata at a level in which are involved the hypoglossal, ambiguus, and spinal accessory nuclei. The lesion is usually vascular in origin.

Durham, Robert H.—Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

When down in the mouth, remember Jonah: he came out all right.—Thomas Edison

Shakespeare's Doctors

Dr. Cornelius

Questions raised but left unanswered constitute one of the most intriguing of literary devices to retain the reader's interest long after his perusal of the script. Just such an engaging speculation arises in "Cymbeline": what was the nature of the drug Dr. Cornelius prepared at the behest of the Queen?

Shakespeare's court physicians had to be artful diplomats as well as doctors, since they must sometimes have been required to follow orders that challenged or compromised their moral integrity.

When the Queen in "Cymbeline" commanded Dr. Cornelius to compound a poison for her to administer experimentally to lower animals, he was faced with an ethical dilemma: adherence to court protocol versus his conscience, which revolted at the Queen's assignment, particularly because he rightly suspected her of ulterior motives. Without qualm, he had often compounded for her various innocuous cosmetics and unguents. But poison! That was another matter!

How did Dr. Cornelius resolve this moral conflict? He tempered obedience with discretion by providing the Queen with a drug that would appear to be lethal but act only as a temporary anesthetic.

> I do not like her. She doth think she has
> Strange lingering poisons. I do know her spirit,
> And will not trust one of her malice with
> A drug of such damned nature. Those she has
> Will stupefy and dull the sense a while,
> Which first, perchance, she'll prove on cats and dogs,
> Then afterward up higher; but there is
> No danger in what show of death it makes,
> More than the locking-up the spirits a time,
> To be more fresh, reviving."*

We cannot but speculate on what the drug may have been. When administered to Imogene it was "murderous to the senses"; further, it made her "primrose-pale" and "stark." While a small dose of chloral could have acted as a narcotic, it would hardly have had such a drastic effect as to make Imogene "primrose-pale" and "stark." Could the drug have been chloroform? But chloroform was not discovered until 1831!

Did Shakespeare foresee the advent of chloroform? Did he possess a quality of seership that provided him with telescopic vision into the future?

*Cymbeline I, 5.

Cured by Shame

The patient was a woman in the King's household who, while bending down to lay the table, was attacked by a sudden "rheumatic swelling of the joints," and was unable to assume an erect posture. The King's physician, being commanded to cure her, and having no medicaments at hand, had recourse to "psychic treatment" and, by removing first her veil and then her skirt, called to his aid the emotion of shame, whereby a flush of heat was produced within her which dissolved the rheumatic humour, so that she stood upright completely cured.*

*Edward Browne, Arabian Medicine.

The Cytologic Evaluation of Early Pregnancy

A Review

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VARIOUS TECHNIQUES are available to the physician for evaluating the status of early pregnancy. These techniques involve a direct or indirect estimate of the pregnancy hormone production. Chorionic gonadotropin and progesterone are the two major hormones produced in early gestation. The trophoblast elaborates chorionic gonadotropin, which acts on the corpus luteum to maintain its production of progesterone. Quantitation of the levels of chorionic gonadotropin in early pregnancy is performed only in specialized laboratories. Progesterone production can be estimated by the amount of pregnanediol, its major metabolite, excreted in the urine and by vaginal cytology. The determination of pregnanediol is difficult, expensive and time-consuming. Vaginal cytological evaluation of progesterone, although possibly not as accurate an index as pregnanediol determination, has a number of advantages.[1-5] Vaginal smears are inexpensive and easily obtained, and the results are available with little delay. Only the most recently exfoliated vaginal epithelial cells are of value in the estimation of the hormonal background of the pregnancy. Cells are obtained from the lateral wall of the proximal vagina with a tongue blade or a moistened cotton-tipped applicator.

Differentiation of Vaginal Epithelium

Proliferation of the vaginal epithelium takes place only in the basal layer; differentiation occurs in the parabasal, intermediate, and superficial layers. Desquamation may occur from any layer. Cellular maturation at the time of desquamation reflects the total hormonal environment affecting the vaginal epithelium. A quantitative estimate of the degree of maturation can be obtained by various indices of the exfoliated cells. The maturation index consists of a differential counting of parabasal, intermediate and superficial cells on the smear. Other indices commonly used are the

karyopyknotic* (pyknotic) index and the eosinophilic (acidophilic) index. Only cells which have intact margins and occur singly or in small clusters are evaluated. Superficial cells with pyknotic nuclei are counted in the karyopyknotic index. Other aspects of hormonal evaluation are judged by the appearance of the exfoliated vaginal cells and the presence of other cells on the smear, such as erythrocytes, histiocytes, decidual and trophoblast cells, Trichomonas vaginalis, Candida albicans and virus inclusion bodies.

The degree of maturation of the exfoliated cells depends on the ability of the vaginal mucosa to respond and the type and quantity of hormonal stimulation. Surgical or radiation damage may alter the response of the vaginal mucosa to hormonal stimulation. Infection, easily recognized by the presence of other cellular structures in the smear, also alters the vaginal mucosa and its ability to respond. Hormonal abnormalities and drugs may likewise affect the vaginal mucosal response and hence the cells that are exfoliated.

Characteristic Hormonal Effects on the Vaginal Mucosa

Estrogen Effect

Endogenous or exogenous estrogen produces proliferation and maturation of the vaginal epithelium with desquamation of superficial cells. These cells have rectangular, transparent cytoplasm with pyknotic nuclei, occur singly, and lie flat on the smear. Only occasional Döderlein bacilli and leukocytes are present. Quantitative estimates are satisfactory indicators of estrogen effect. The karyopyknotic index is most frequently used, as it is relatively uninfluenced by technical errors.[6] Estrogen effect on the vaginal mucosa may be seen alone or with that of progesterone.

Progesterone Effect

Progesterone also has a marked effect on the vaginal mucosa, but this effect is never found in the normal woman unless there is simultaneous estrogen stimulation. Progesterone, with estrogen, results in the differentiation and exfoliation of intermediate cells which also have rectangular, transparent cytoplasm but contain vesicular nuclei. When progesterone effect predominates, the exfoliated intermediate cells are found in clusters, the cell margins are folded and indistinct and Döderlein bacilli and leukocytes are numerous.

Vaginal Cytology in Pregnancy

Early Pregnancy

The hormonal status of the pregnancy is reflected by vaginal cytology.[7,8] In the first trimester the vaginal cytologic changes are the result of hormones produced primarily by the corpus luteum. Because hormone production may fluctuate, the vaginal smear may vary to a moderate degree and still be normal. During the second and third trimesters the vaginal epithelium responds to hormone production of the placenta.

In the luteal phase of a normal menstrual cycle, there is proliferation of cells in the intermediate cell layer. Regression follows if conception does not occur. With pregnancy, the proliferation of the intermediate layers continues and the cytoplasm of the intermediate cells fills with glycogen.

Ten Weeks Gestation

A normal pregnancy smear is dependent upon the production of large quantities of estrogen and progesterone, the effect of the latter predominating.

After approximately ten weeks gestation, glycogen is usually present in the cytoplasm of the intermediate cells and causes condensation of cytoplasm at the cell borders which then appears as a thickened cell membrane. The nucleus is frequently flattened and eccentrically located at the cell margin. These changes characterize the pregnancy or navicular cell.[9] Only intermediate and superficial cells are exfoliated in a normal pregnancy. The parabasal cells, which are small and round or oval, have deep-staining cytoplasm, and vesicular nuclei are not normally found on a pregnancy smear. In the first trimester the karyopyknotic index progressively decreases and should be less than 30 percent. After the first trimester it is

*See Test Your Word Score Page 649.

under 10 percent. Superficial cells may have folded cell margins (Table 1). Cytolysis is common in pregnancy and, although not a poor prognostic sign, makes hormonal evaluation difficult. Cytolysis is usually the result of infection and may be eliminated by local vaginal antibiotic therapy.

TABLE 1
Normal Pregnancy Cytology

A. Objective criteria
   1. Intermediate and superficial cells
   2. No parabasal cells
   3. Karyopyknotic index, first trimester, less than 30%
   4. Karyopyknotic index, last two trimesters, less than 10%
B. Subjective criteria
   1. Navicular cells
   2. Intermediate cells in clusters
   3. Folded and indistinct margins of intermediate cells
   4. Folded margins of superficial cells
   5. Leukocytes and Doderlein bacilli

Dead Fetus

The vaginal smear may arouse suspicion that the patient is pregnant; but in a smear without the usual findings, pregnancy is unlikely. When the status of a pregnancy is in doubt, exogenous estrogen in moderate dosage will not change the smear if the gestation is normal.[7] If the *conceptus* is dead and the placenta no longer functioning, exogenous estrogen will cause an increase in exfoliated superficial cells and therefore in the karyopyknotic index. Smears in some non-pregnant patients may be similar to those of pregnancy; hence quantitative estimates are of minimal help.

Castrated and Menopausal Women

Smears from castrated young women and menopausal patients also have only occasional superficial cells but do not show the other effects of progesterone. Similar smears are found in patients with amenorrhea due to low follicle-stimulating hormone production. Because progestogen treatment produces cells which on the smear are indistinguishable from those of pregnancy, the cytologist must have clinical data if the vaginal smear is to be interpreted adequately.

Serial vaginal smears are of greatest value in the evaluation of patients who have had previous spontaneous abortions, who have clinical signs of a pregnancy abnormality, who are receiving hormonal therapy, or who have other complicating disease which increases the risk to the fetus.

Threatened Abortion

The vaginal smears of patients with threatened abortion due to hormonal abnormalities have an increasing karyopyknotic index, thinning and separation of the intermediate cells, and disappearance of navicular cells and Döderlein bacilli (Table 2). Because cytologic changes in a hormonally-disturbed pregnancy appear before the clinical signs and symptoms, the values of cytologic evaluation in certain asymptomatic patients is obvious. Smears from patients with inevitable abortion show the findings of a hormonally disturbed pregnancy as well as erythrocytes, histiocytes and occasionally decidual and trophoblast cells.

TABLE 2
Pregnancy Cytology
Hormonally Disturbed Pregnancy

A. Karyopyknotic index
   1. Increasing in first trimester
   2. Greater than 30% in first trimester
   3. Greater than 10% after 14 weeks
B. Thinning and separation of cell clusters
C. Disappearance of navicular cells
D. Disappearance of Doderlein bacilli

Missed Abortion

The vaginal cytology of missed abortion is usually characteristic. In addition to the cytological pattern associated with threatened abortion, increasing numbers of parabasal cells are found. With delay in expulsion of the products of conception, there is a gradual shift in the type of cell that indicates a return to a predominantly estrogen effect. Because progesterone or progestogen treatment does not alter the cytologic picture in missed abortion, the vaginal smear is of value in determining which patients carry viable pregnancies.

Induced Abortion

In a spontaneous abortion the decreasing progesterone effect precedes the appearance of clinical signs. When the abortion has been induced, however, the corpus luteum, the placenta, or both are usually functioning normally until the moment of interruption. A vaginal smear obtained at this time or shortly thereafter will be normal except for the presence of

erythrocytes, leukocytes, and possibly decidual and trophoblastic cells. The regressive changes in the vaginal smear of an induced abortion usually occur five to seven days after the interference.

Prognostic Significance

A vaginal smear obtained on the initial prenatal examination is of prognostic significance.[4,6,7,10] Over 95 percent of the patients with normal vaginal cytology and no clinical abnormalities will deliver a living viable infant. Those with normal vaginal cytology who do have clinical evidence of threatened abortion also have a good prognosis. An abnormal smear from a patient without clinical evidence of threatened abortion indicates an increased risk for the fetus, a successful outcome occurring in about 65 percent of these cases. However, when vaginal cytology is abnormal and clinical signs of threatened abortion are present, only about 30 percent will deliver living viable infants.[7] Serial smears therefore are desirable for more accurate evaluation.

Discussion

A number of studies have correlated vaginal cytology with pregnancy hormone excretion.[1,3,5] Chorionic gonadotropin excretion directly reflects the condition of the trophoblast. Urinary pregnanediol excretion and vaginal cytology estimate production of progesterone by the corpus luteum in early pregnancy and by the placenta in the last two trimesters. After the 20th week, maternal estriol excretion indicates the well-being of the fetus. The evaluation of chorionic gonadotropin, pregnanediol and estriol excretion, as well as vaginal cytology, would give the most accurate prognostic estimate for a pregnancy as well as an indication of the site of the abnormality. Changing of the vaginal smear in abortion reflects a disturbance in estrogen-progesterone balance rather than an increase in estrogen activity.[11]

References may be secured from the author or the reprints.

Although 20 percent of all pregnant women bleed in early pregnancy, only one half of these will abort. Thus bleeding is not always an indication of an abnormal gestation and a sign of impending abortion. Germ-plasm defects, chromosomal abnormalities and non-hormonal factors are responsible for the majority of these early pregnancy losses. Hormonal abnormalities probably account for only 5 percent of all spontaneous abortions.[10] Only in this group with hormonal abnormality is the vaginal smear of value, as the smear pattern may identify this problem in sufficient time to salvage the pregnancy with appropriate hormonal replacement therapy. Treatment with hormones is wasted on threatened abortion due to any other etiology. Prognosis for pregnancy is poor only among those who have had three or more consecutive abortions. Hormonal therapy not only cannot improve the salvage in the great majority of these patients but may result in a missed abortion. When therapy is associated with an improved vaginal smear, the prognosis is excellent. In a non-viable pregnancy, estrogen therapy results in an increase in the karyopyknotic index, whereas progesterone and synthetic progestogens do not affect it. The prognosis is good only if the smear returns to normal.

Conclusion

The vaginal smear offers the clinician an available tool with which to evaluate the hormonal status of early pregnancy. Cells for the smear are readily obtained. Cell studies can be repeated frequently, are relatively inexpensive, and are available with little delay.

Vaginal smears are of prognostic value if serial studies are obtained from those patients who have had previous pregnancy losses, who have clinical signs of threatened abortion, and who are receiving hormone therapy. Hormone therapy, although commonly used, has limited application and may be expected to improve fetal salvage in only the small percentage of patients with threatened abortion secondary to a hormonal deficiency.

Silence

Better to remain silent and be thought a fool than to speak out and remove all doubt.—Abraham Lincoln

Autogenous Tooth Transplantation*

HOWARD P. BOLLER, D.D.S.
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TISSUE GRAFTS and transplantation of various organs or body tissues are common and well established practices in medicine and surgery and also in the fields of dentistry and oral surgery. Skin and bone grafts about the mouth and jaws have been as common to oral surgery as tissue grafts have been to general surgery, and more recently there have developed techniques for the transplantation of teeth. Certainly if some tissues or organs can be transplanted, why not a tooth?

Stories have been written in the early days of medicine and dentistry about a tooth being removed from one person and implanted in the jaw of another, but the length of time for retention or service of these implanted teeth was usually omitted. It is known that this procedure cannot be successful, as the implant will be rejected by the recipient tissue and be exfoliated or absorbed.

Vital Tooth Buds

The Wisdom Tooth

There is a type of tooth transplant that has been successful: the autogenous transplant of vital tooth buds. Although any tooth in the proper stage of development theoretically might be transplanted, the most common and useful transplant is the third molar, or wisdom tooth. During the teen ages the third molars are beginning to develop their roots and the eruption process begins; in many instances, however, there seems to be insufficient room for these last molars to erupt, thus resulting in impacted and non-functioning teeth. Since various complications frequently result from such impacted teeth, it is advisable to have them removed surgically.

The Six year Molars

The first molars are probably the most important individual teeth and are referred to as the "keys to occlusion." But since they

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Fig. 1—Impacted molar to the left and carious third molar to the right, pre-op.



Fig. 2—Tooth transplant three days post-op, roots incompletely grown.



Fig. 3—Tooth transplant five years post-op with caries in neglected second molar.

erupt at the early age of six years when oral hygiene and proper nutrition are difficult problems, these teeth have a high mortality rate through dental caries. Deterioration may continue if they are left untreated until the mid-teens and finally, one or more of these first molars may need to be extracted.

Thus the situation is frequently presented where an important tooth must be removed due to caries and infection, and a healthy but malpositioned tooth may be transplanted and become useful.

Selection for Autogenous Transplant

Autogenous transplant cases should be selected carefully. There are certain conditions that must be met in order to insure success. (1) The transplant must be a developing tooth with the roots only partially complete. (2) There must be no acute infection. (3) The developing root apices with their vital embryonal membranes must be undisturbed. (4) Near isothermic and isotonic conditions must be maintained during transplantation. (5) There must be adequate space to receive the transplant and this space must be maintained during eruption. (6) Some method of retention and protection of the transplanted tooth during healing must be provided.

Developing Tooth Bud

Fully formed teeth receive their nourishment and vitality by means of small vessels and nerves entering the foramina at the apical ends of the roots, but these vessels and nerve connections are not established until the root is almost completely developed. The developing tooth bud receives its nourishment primarily from the dental follicle in which it grows and from surrounding bone. Therefore the incompletely developed tooth can be carefully moved to a new site and will establish the necessary vascular supply in an organizing blood clot around the transplant.

The Follicular Sac

It has been proven that calcification of the crown is complete by the time two to three millimeters of root have developed. At this stage, the follicular sac around the crown, which is usually injured in the process of re-

moving the transplant, is no longer needed and may be removed. Continued growth depends upon the placement of the transplant at the proper depth and upon allowing growth by eruption into functional occlusion. Vitality depends upon the re-establishment of the vascular supply to the dental pulp and periodontal membrane attachments. Innervation may or may not occur in transplants; but this is not important.

Fully Formed Teeth

Transplanting fully formed teeth has been attempted, but ultimately root resorption occurs even though the procedure is an autogenous transplant. Vascularization essential to maintain a vital tooth is difficult or impossible to re-establish in a fully formed tooth; therefore, tooth structure not receiving a nourishing vascular supply will decompose and become infected. This has occurred also in reimplantation of traumatically avulsed teeth. Even though root-canal sterilization and filling with an inert material has been carried out for these avulsed teeth, resorption will take place and the reimplant will ultimately fail.

The Technique

The surgical procedure for these transplants is basically a combination of two operations: extraction of a diseased tooth, and surgical removal of the impacted and unerupted tooth bud to be placed in the prepared site of the removed diseased tooth.

Removal of the Tooth Bud

A typical case of a lower third-molar (wisdom tooth) bud transplanted to the first molar site is carried out as follows: An incision through the mucoperiosteum is made from the distobuccal region of the developing third molar anteriorally along the crest of the ridge to the distobuccal of the second molar and around the gingival margin of second and first molars. The mucoperiosteal flap is freed and elevated to allow adequate access. Bone overlying the third molar is removed with chisel or surgical bone bur sufficient to permit elevation and atraumatic removal of the tooth bud. Then it is left in its crypt to await transplant.

Preparing the Socket

The diseased first molar is then removed and the site prepared by removal of interseptal bone and enlargement of the socket with chisel or bur.

Transfer to Host Site

The transplant is now removed carefully from its crypt and transferred to the host site. It should be placed in approximately the same depth as it was found in its own crypt since the length of root growth will depend to some degree upon the distance it moves as it erupts into occlusion. The third molar socket is cleaned up by removing bone fragments, smoothing sharp edges, and removing dental follicle remnants. Then the mucoperiosteal flap is replaced and sutured.

Immobilization

Retention of the transplant is effected by means of silk sutures or wire crossing over the crown surface, extending from second molar to bicuspid. Surgical packs or acrylic splints are useful and often used, especially for lower posterior transplants.

Postoperative Care

The patient is instructed in general mouth care, diet and analgesics. Antibiotics are not routinely given, as was originally thought necessary. Postoperative x-rays are taken at completion of the operation and then at various monthly intervals as desired to follow growth and eruption.

Comments

It is quite common for the root canals and pulp chambers of transplanted teeth to become partially or completely filled in and obliterated by radiopaque tissue. Histologic studies of this tissue show that it is different from normal or secondary dentin. It is possible that the tissue within the pulp chamber is replaced by connective tissues in growth; thus the odontoblasts that lay down dentin are replaced by cells of inferior differentiation which deposit osteodentin and bone rather than the normal tubular dentin. Clinically this is of no significance as long as it occurs only within the

tooth, since the tooth seems to retain a healthy and functional state even without pulp chamber or root canals.

Conclusion

I would like to point out that autogenous transplantation of developing tooth buds is not only possible but is being done by many oral surgeons at the present time.

It is applicable mainly in teenagers.

Fully formed teeth cannot be transplanted with permanent success.

New Superstitions Still Popping Up

Old superstitions, unlike old soldiers, do not fade away. They are replaced by new superstitions and new misconceptions, says TODAY'S HEALTH GUIDE, the American Medical Association's manual of health information for the American family.

This is particularly true of superstitions and misconceptions about health. New scientific advances and discoveries breed a whole new crop of health superstitions.

Some of the new ones cataloged in the health book are—

Today, we have the mistaken idea that necessary and harmless chemicals used in processing foodstuffs may cause mysterious diseases like cancer. (They won't.)

We see people afraid to cook with aluminum utensils for fear of poisoning the food. (They will not.)

We observe people who refuse to wear glasses, and others who shun much-needed hearing aids. (Both are completely accepted by society today.)

People oppose fluoridation of public water supplies because the same chemical has also been used for poisoning rats, overlooking the fact that the whole difference lies in the matter of dosage. (Fluoridated water is completely safe.)

Many people blame climatic changes on the atomic bomb; past generations attributed such changes to artillery fire, to the use of radio and television. (The bomb has not changed climate.)

Countless mothers live in fear for their children's lives because a heart murmur had been reported. Although murmurs should be checked by a physician most heart murmurs are harmless.

There is still active opposition to the use of immunizing procedures, such as vaccination and immunization, because of superstitious dread of introducing a poison into the system. (The vaccines now in general use are safe.)

There is a modern cult of naturalism which holds that only "natural foods" are wholesome because foods grown with the aid of chemical fertilizers are inadequate. (This isn't true.)

Many harbor prejudices against canned or frozen or otherwise processed foods, and even advocate eating raw food exclusively. (Processing does not affect foods substantially, nor does proper cooking.)

There is one thing more exasperating than a wife who can cook and won't, and that's the wife who can't cook and will.—Robert Frost

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Faith may be defined briefly as an illogical belief in the occurrence of the improbable.—H. L. Mencken

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Love is the triumph of imagination over intelligence.—H. L. Mencken

Cardiorespiratory Endurance

Before and After Regular Physical Activity*

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EACH YEAR MORE and more members of our affluent society avail themselves of an opportunity to participate sporadically in seasonal sports such as skiing. While many of the participants have been regularly active throughout their lives, most will be characterized by sedentary living patterns which predispose them to a greater risk of accident and of cardiovascular distress while performing sudden, strenuous physical exertion. Although proper physical conditioning may reduce the risk factor, there is little evidence available documenting the physical-fitness levels of middle-aged American men. This report is concerned with the physiologic observations recorded on a middle-aged man while he was sedentary and at periodic intervals after he initiated and maintained a program of regular physical activity. In addition, the methods used to assess his performance capacity are described.

Case Report

The subject was 48 years old when he volunteered for the study. After an appropriate history and physical examination he performed a standardized multistage treadmill test[1] in which he began walking at a speed of 3.4 mph on a one-per-cent grade. The speed remained constant while the slope of the treadmill bed was elevated one percent per minute. Blood pressure and pulse rate were measured by the auscultatory method during the last half of each minute, and a single lead electrocardiogram was recorded continuously by radiotelemetry.[2] Minute ventilation was measured during inspiration from a Tissot respirometer, and oxygen consumption was determined by the Douglas-Haldane method during every other minute. Walking was stopped when the pulse rate reached 180 beats per minute or earlier if he was dyspneic or had chest discomfort.

Following the initial evaluation he began a program of interval training during which he jogged one quarter of a mile in approximately 2½ minutes, walked an equal distance, and resumed jogging at the original pace for another quarter of a mile. He spent approximately 20 minutes a day performing this in-

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termittent program during the first six months. At that time he was re-evaluated on the treadmill in the same manner. As his physical condition improved he increased the distance jogged and decreased the duration of the recovery period. Eventually he negotiated two miles comfortably in approximately 18 minutes, subsequently increasing the distance gradually until he could jog comfortably four miles continuously in 32 to 36 minutes each day. It was estimated that his oxygen requirements for maintaining this pace were approximately 45 ml/kg, or about 12 to 13 times those of the resting metabolic state, and his estimated caloric expenditure during the four-mile sessions was between 400 and 500 kcal. He was re-evaluated on the treadmill at six-month intervals. For purposes of this report, the physiologic responses recorded during the first 12 minutes of each evaluation prior to and after six and 24 months of training will be compared.

Results

Aerobic Working Capacity*

During the initial examination pulse frequency reached 180 beats per minute on a 14-per-cent grade where the oxygen uptake was 34.6 ml/kg. This value approximated that recorded previously in a group of sedentary middle-aged men of comparable age.[3] During the next two years a gradual and steady increase in the aerobic working capacity was recorded and related to the quality and quantity of the activity program. After six months of regular physical activity, during which he performed interval training, the aerobic working capacity increased from 34.6 to 39.6 ml O_2/kg; after performing a steady-state jog of three to four miles at least three times a week the aerobic working capacity increased approximately an additional 7.0 ml O_2/kg. *Therefore, after two years of regular physical activity the peak aerobic working capacity increased from 34.6 to 46.2 ml O_2/kg, reflecting an overall increase in oxygen consumption of approximately 850 ml.*

Ventilation

The ventilatory volumes recorded while standing were slightly higher during each evaluation than those usually recorded in healthy men, and varied from 24.9 L/min during the initial study to 18.3 L/min when studied two years later. During each study a striking elevation of the minute ventilation during the initial four minutes of walking was recorded (Figure 1). This was followed by a decrease of the ventilatory requirement during the next three to six minutes of walking, and finally by a gradual increase during the latter part of each test. A volume of 90.9 L/min was recorded at an oxygen requirement of 31.3 ml/kg during the twelfth minute of the first test. This response indicated that the large ventilatory volumes recorded during the low levels of physical effort were induced by a combination of psychological and physiological adaptations to the treadmill test rather than solely by the metabolic demands. During subsequent evaluations the same relative pattern of over-ventilation during the early minutes of walking followed by a marked decrease in the ventilation at the higher oxygen requirements persisted. This was especially noticeable during the third evaluation when the minute ventilation recorded while walking on a 12-per-cent grade was 50.8 L/min compared to 56.0 L/min at an oxygen requirement of only 14.9 ml/kg. These findings indicated the importance of evaluating subjects objectively under a moderate degree of physical stress prior to making judgments about their ability to exercise satisfactorily. *The values recorded in this subject after two years of regular physical activity on the 10- and 12-per-cent grade indicated that a marked increase in ventilatory efficiency developed during the process of physical conditioning.*

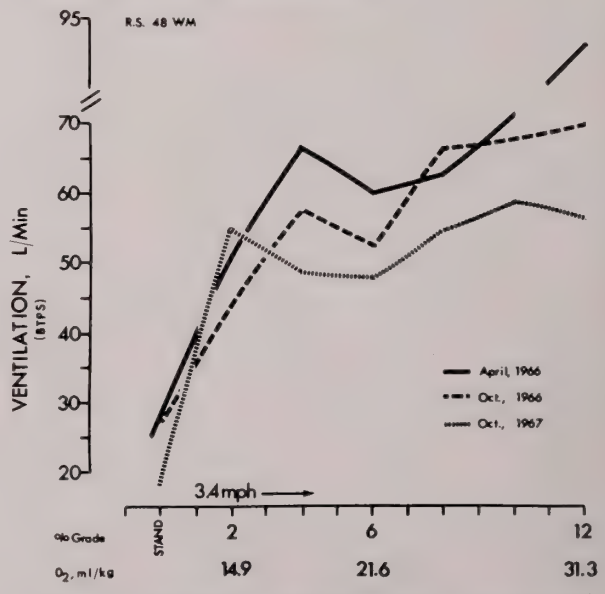


Fig. 1—Ventilatory responses before, during and after two years of regular physical activity.

*See Test Your Word Score Page 649.

Pulmonary Functions

Pulmonary functions were normal before initiating training (Table). These values remained essentially unchanged from one test to the next.

TABLE
Pulmonary Function Studies

	Total Vital Capacity (Liters)	1-Second Vital Capacity (Liters)	Maximum Voluntary Ventilation (L/min)
April, 1966	4.9	3.7	164
October, 1966	5.0	3.6	166
October, 1967	4.7	3.9	132

Blood Pressure

The resting blood pressure measurements were essentially normal upon entering the study. During the initial evaluation a characteristic, gradual increase of the systolic blood pressure accompanied each increased oxygen requirement (Figure 2). A peak value of 215 mm Hg was recorded during the twelfth minute of walking. At each subsequent evaluation substantially lower systolic blood pressure levels were recorded while resting and during exercise. Additional lowering of the systolic blood pressure occurred when the activity program became more strenuous. These changes in systolic blood pressure indicated that the systolic work of the heart and the oxygen cost of cardiac work had decreased at comparable levels of energy expenditure during the study.

During the initial study the diastolic blood pressure increased during walking approximately eight to ten mm Hg. However, two years later, although the resting diastolic blood pressure had not changed substantially, there was a decrease of this value during comparable levels of treadmill walking. *These latter changes indicated that a decreased peripheral vascular resistance had accompanied the training process* (Figure 3).

Pulse Rate

Pulse rates are generally regarded as the most objective means of evaluating an individual's state of physical fitness. Once again, as in the other physiologic measurements, significant reductions in the pulse rate during rest and throughout the treadmill test were recorded at each subsequent evaluation. The resting pulse rate decreased from 80 beats per minute initially to 56 beats per minute two years later; on a 12-percent grade these values decreased from 168 to 128 beats per minute. *These decreases indicated that a greater extraction of oxygen was accomplished per stroke beat after training and supported the concept that regular physical activity stimulates the development of cardiovascular efficiency* (Figure 4).

Discussion

The ability to cope with physical stress is a subject of import to every individual. Few people would argue that the safe performance

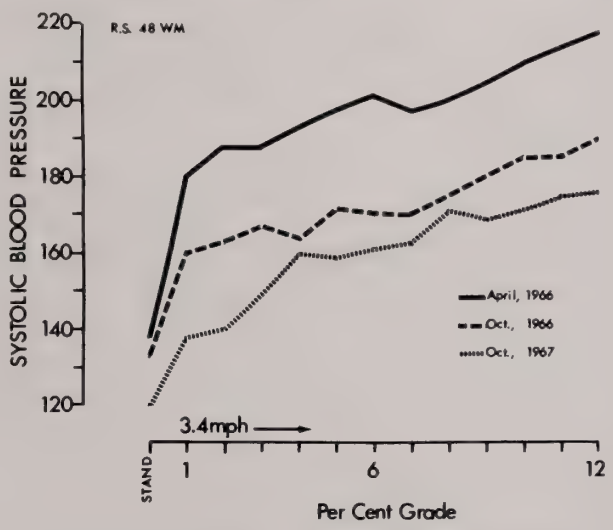


Fig. 2—Systolic blood pressure responses during treadmill walking.

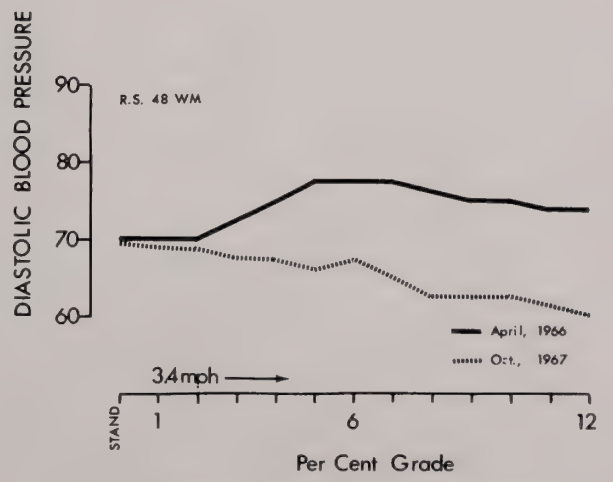


Fig. 3—Diastolic blood pressure responses.

of acceptable forms of physical recreation demands maintaining some level of physical fitness. However, measuring a subject's physical fitness readily and accurately poses a problem for many physicians. The test described here is an example of one of many graded exercise tests with which physicians can quantitate physical fitness. In addition to measuring the aerobic working capacity the physician can evaluate the quality and the quantity of the cardiorespiratory adjustment to the gradually increased workloads. While many physicians might find a treadmill an impractical instrument, a similar evaluation can be administered either with a stepper[3] or with a bicycle ergometer. It is obvious that for most clinical situations, a submaximal test in which the cardiorespiratory adjustments to gradually increased oxygen requirements are recorded simultaneously may provide enough information for the objective assessment of an individual's endurance capacity.

Although the relationship of physical fitness to health status is not known, it might be speculated that sports injuries are less frequent in better trained participants who do not fatigue readily. The patient depicted in this study was chosen because the responses recorded before and after regular physical activity approximated the mean values recorded in a larger group of men of comparable age. The findings illustrated many of the advantages of an "active physical examination." Although regarded as healthy by the usual clinical standards, the initial aerobic working capacity was average for men of his age, indicating that he could jog approximately 142 meters per minute or a mile in about ten minutes aerobically. Evidence of increased cardiorespiratory efficiency accompanied the activity program. When retested two years later the aerobic working capacity was 46.2 ml/kg, a capacity more than adequate for pursuing a distance of two miles in 15 minutes. It might be speculated that safe performance in competitive sports such as skiing was better assured after the training program than before. Similar alterations in functional adjustments to graded exercise were recorded in other healthy men who participated in a similar program.

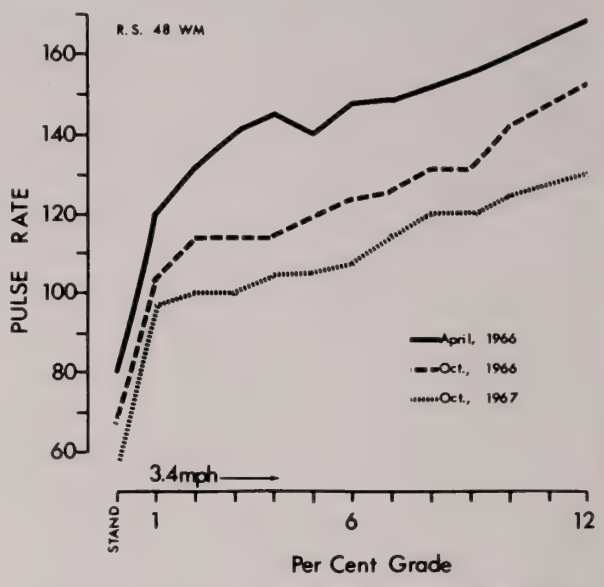


Fig. 4—A decreased pulse rate was recorded at rest and throughout walking at comparable levels of work as a result of the training program.

These findings also indicated that the trend toward a decreased oxygen capacity with age might either be delayed or even be reversed. For instance, several investigators[4,5,6] have reported a decreased physical working capacity in aging populations. Andersen and Hermansen[7] recorded peak oxygen consumption values of 34.0 to 36.0 in Scandinavian office and industrial workers between the ages of 50 to 54 years, and of 48.0 ml/kg in regular skiers of comparable age. The subject reported here demonstrated that it is possible to move from one category to the other with a program of regular physical activity.

Many types of endurance programs are conceivable and, as such, could be prescribed to meet each individual's specific requirements. Of the possible ways to increase endurance, jogging is probably preferable, since it can be performed almost anywhere with relative ease; requires very little expense and equipment; allows an individual the opportunity to pace himself; and at the same time taxes the cardiorespiratory system adequately. Pulse rates between 145 and 160 beats per minute are usually recorded in individuals during the type of program described here. Psychologically, many individuals react against jogging because they don't want to be the "lonely runner." These objections are usually handled if the

individual is properly instructed prior to initiating training. He should be informed that jogging the distance aerobically is more important than the speed, and that such programs are usually conducted regularly in YMCAs throughout the United States. Correlating the energy expenditure with the distance covered may also be of value. For instance, the person who performs to a 20-per-cent grade at 3.4 mph has an aerobic working capacity approximating 45 ml O_2/kg, a value roughly equivalent to the oxygen requirement of jogging one mile in eight minutes. The energy required to negotiate a mile would approximate 125 kcal. Therefore, a jog of three miles in 27 to 30 minutes would require an expenditure of 375 to 425 kcal.

Deconditioning is an additional indication for assessing an individual's aerobic working capacity. Since this often occurs as a result of an accident during physical activity, the objective assessment would be a measure of changes away from conditioning as well as toward conditioning.

Summary

The physical working capacity and cardiorespiratory adjustments to gradually increasing levels of physical exercise were measured in a 48-year-old healthy white man before he initiated an extended program of regular physical activity. He was retested at six-month intervals. His course was characterized by a subjective sensation of improved well-being and by objective evidence of improved cardiorespiratory efficiency, as well as by a substantial increase of his oxygen uptake from 34.6 to 46.2 ml/kg.

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Kurt Schnitzer, M.D.*

Doctor Schnitzer practices general medicine in Santa Ana, California. He is a native of Vienna, Austria, where he received his medical training. Forced to leave Austria by the Anschluss, he fled to Santo Domingo where he eked out a living as a photographer; and he eventually had assignments from *"Harper's Bazaar," National Geographic," "Saturday Evening Post," and "N. Y. Times Supplement."*

Reaching the United States in 1944 he worked to become a licensed physician, and has since become a leader in his community, recently serving as President of the Orange County Academy of General Practice.

He has maintained his interest and proficiency in photography. The current cover photo, "The Non-Conformist," won first prize in its category in the 1967 American Physicians Art Association meeting in Atlantic City.

*See cover photograph.

A man will sometimes devote all his life to the development of one part of his body—the wishbone.—Robert Frost

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Revelation

The short skirts of today reveal the malnutrition of yesterday.—Don Herold

Surgical Detour

The Sklifosovsky Institute took in a new patient. He was nineteen years old and came from Sverdlovsk. Seven years previously the boy had swallowed some crude hydrochloric acid, which he mistook for water.

The esophagus stricture developed slowly but surely. To avert a total stricture doctors tried passing bougies, or special bulbous instruments, which were meant to dilate it. But that was of little help. The youth had to be fed through a stomach fistula. The doctors in Sverdlovsk tried to render more effective help and create a new esophagus. But the operation was unsuccessful.

At the Sklifosovsky Institute Professor Petrov examined the youth with utmost care. There were scars—marks of a surgeon's knife—on the patient's neck and chest.

A few days later the youth was put on the operating table. The surgeon opened up the abdominal cavity and drew out about 12 inches of the small intestine. He cut it at both ends with true surgical precision, detaching it from the bowels. Then he joined the two open ends of the bowels and thereby restored their continuity.

The excised piece of the small intestine had not lost all its connections with the bowels. Some blood vessels led to it from the mesentery. . . . If the vessels had been cut, the excised section of the intestine would be deprived of its blood supply and would soon perish.

The surgeon made a special tunnel-like passage under the skin of the chest. With the help of instruments specially designed at the Institute, he detached the skin from the underlying tissue all the way from the cut in the abdomen to the left collar-bone and the neck. This formed a subcutaneous tunnel. The excised intestine was carefully drawn into this tunnel. The tunnel was like a casing for it. One end of the intestine came to the surface on the neck, in line with the upper section of the esophagus.

The operation entered its second, no less important stage. The surgeon cut open the neck, bared the esophagus, and drew it out. He sutured the intestine into an opening in the wall of the esophagus above the stricture.

So much for the top end of the excised intestine. The bottom end, meanwhile, had been previously sewed into the stomach below the stricture. The excised section of the small intestine thus connected the topmost part of the esophagus with the stomach.

The operation on the youth was made in 1942. Before and after it, Professors Petrov, Arapov, Rozanov, and others of the Sklifosovsky Institute, performed hundreds of similar operations. A great many operations of this kind were since performed in other cities of the Soviet Union.*

*L. Fridland, M.D.: The Achievement of Soviet Medicine, 1961, edited and translated by W. Horsley Gantt, M.D.

Taxes

Taxation: the process by which money is collected from the people to pay the salaries of the men who do the collecting. The surplus is used to pay the salaries of the men the people elect to decide how much shall be collected from them.*

*Jacob Braude: Speaker's Encyclopedia

Hyponatremia

Increased Antidiuretic Hormone and "Inappropriate" Thirst in a Patient with Bronchogenic Carcinoma*

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A DEPRESSION OF the serum sodium concentration below 135 mEq/L or of the serum osmolality below 270 mOs/kg. of water indicates excessive water for the amount of solute in the body. The serum sodium concentration is regulated by the thirst-neurohypophyseal-renal axis, and hyponatremia always suggests dysfunction of one or more components of this regulatory system.

An increased water intake causes hyponatremia only when associated with dysfunction of the neurohypophyseal-renal system. Normally an increased water intake inhibits antidiuretic hormone release, tubular reabsorption of water is decreased, and a dilute urine eliminates the excess water from the body. Following diuresis the expanded plasma volume and decreased osmolality return to normal and antidiuretic hormone release again permits the elaboration of an appropriately concentrated urine.

The role of thirst in this homeostatic system is frequently overlooked. The patient to be described was unable to elaborate a dilute urine, while large quantities of an antidiuretic hormone-like material (probably antidiuretic hormone) were produced by the cells of a bronchogenic carcinoma. However, a normal serum osmolality could have been maintained had the subject appropriately curtailed his fluid intake. That he did not do so suggests that, under these circumstances, his thirst was "inappropriate."

Report of A Case

The patient, a 62-year-old white male executive, was admitted to the Indiana University Medical Center on 8-29-65 because of fatigability and headaches. These complaints were attributed to a fall incurred five months previously that caused injury to his head and chest. Physical examination was normal on admission. An initial chest roentgenogram demon-

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strated a right lateral chest density suggesting a loculated pleural effusion or hematoma at a location which coincided with the site of previous injury.

Low Serum Sodium Concentration

The initial serum sodium concentration was 128 mEq/L and the serum chloride concentration, 88 mEq/L. These and additional laboratory studies are summarized in the Table. Various diagnostic procedures, including cerebral angiography, were compatible with the diagnosis of a right subdural hematoma, and on 9-13-65 a craniotomy was performed and a subdural hematoma removed. Microscopic examination of the resected tissue was not remarkable. However, hyponatremia persisted throughout the initial period of hospitalization. Because of the unresolved pleural density, chest roentgenograms were obtained repeatedly, and on 1-22-66 the existence of a right hilar mass became apparent.

High Antidiuretic Hormone

The patient was admitted to the hospital for the second time on 1-27-66. The serum sodium concentration was abnormally low and the urine contained an increased amount of sodium. The blood antidiuretic hormone concentration was found to be 12.5 μU/ml. The normal value for blood antidiuretic hormone in the seated adult human male is 1.6 ± 0.6 μU/ml. as assayed in our laboratory[1] using a modification of the method described by Yoshida et al.[2] Share[3] has shown that such methods extract and isolate a substance identical with antidiuretic hormone. An exploratory thoracotomy was performed on 2-4-66 which revealed an inoperable undifferentiated bronchogenic carcinoma. Tissue was obtained for bioassay of antidiuretic hormone as well as for routine histologic examination. On bioassay the tissue contained 525 microunits of antidiuretic hormone per mg. of tissue. The serum sodium concentration was 118 mEq/L on the second postoperative day although the patient had a daily fluid intake not exceeding 2,000 ml. The urinary output varied from 500 to 750 ml. per day. Serial weights of the patient are not available, and urinary sodium and total solute excretion were not measured during this period of hospitalization. Radiation therapy was begun on 2-10-66 and radiologic evidence of a tumor mass promptly disappeared. An antidiuretic hormone level on 3-14-66 was 1.7 μU/ml. of blood at a time when the serum sodium concentration and serum osmolality were normal. The patient was discharged on 3-18-66 and was followed in clinic.

On 8-30-66 his serum sodium and osmolal concentrations were again below normal, and a chest roentgenogram demonstrated a nodular lesion somewhat peripheral to the site of his previous radiation

TABLE I

Date	Bl. ADH μU/ml.	P_{Na} mEq/L	P_{Cl} mEq/L	P_{Osm} mOsm/L	U_{Na} mEq/L	U_{Cl} mEq/L	U_{Osm} mOsm/L	U_{Osm} P/Osm
8/29/65		128	88					
9/ 4/65		126	90					
9/13/65	CRANIOTOMY—Subdural hematoma evacuated							
9/20/65		131	99		84			
9/22/65	DISCHARGE #1							
1/27/66	ADMISSION #2							
1/27/66		130	93		165			
1/28/66	12.5							
2/ 4/66	THORACOTOMY—Bronchogenic carcinoma contaned 525 μU of ADH mg.							
2/ 6/66		118	70					
2/10/66	RADIATION THERAPY BEGAN							
3/14/66	1.7	141	101	272	224	219	816	3.00
3/18/66	RADIATION THERAPY COMPLETED—DISCHARGE #2							
4/ 9/66		143						
8/30/66	ADMISSION #3							
8/30/66	5.7	124	91	257	199		844	3.28
8/31/66	CHEMOTHERAPY BEGAN							
9/ 6/66	2.5	136	93	267	136	124	763	2.86
10/18/66	1.5	142	98					
10/20/66	DISCHARGE #3—Clinical remission							

therapy. He was readmitted to the hospital for chemotherapy. The blood antidiuretic hormone level on 8-30-66 had risen to 5.7 μU/ml., an abnormally elevated value. Following chemotherapy, radiologic and chemical evidence indicated that his disease process had again improved. The blood antidiuretic hormone level fell to 1.5 μU/ml. and the serum sodium concentration was normal. The patient was discharged from the hospital for the third time on 10-20-66, only to be re-admitted approximately three weeks later with the symptoms of cerebral metastases.

He died approximately one month later. Postmortem examination demonstrated diffuse intracerebral metastases of an anaplastic carcinoma with some residual evidence of undifferentiated bronchogenic carcinoma in the mediastinal lymph nodes.

Discussion

Schwartz and his associates[4] reported a syndrome of hyponatremia associated with bronchogenic carcinoma and attributed the hyponatremia to "inappropriate" antidiuretic hormone production. Many investigators have made similar observations, reviewed recently by Bartter and Schwartz[5]. Initially the source of the increased antidiuretic hormone was speculative. Recently however, Amatruda and his associates[6], as well as others[5], have demonstrated that such tumors may contain, and presumably release into the circulation, large quantities of antidiuretic hormone or an antidiuretic hormone-like substance. The present case, as well as the cases reported by Tisher[7] and by Utiger[8], demonstrate that an elevated blood antidiuretic hormone level and the associated hyponatremia can be corrected by treatment of the tumor. In our patient and the patient of Tisher, hyponatremia recurred upon recurrence of the tumor. It seems to be established that certain bronchogenic tumors do produce and release into the circulation antidiuretic hormone or an antidiuretic hormone-like material.

Naturesis

Renal salt loss, unrelated to either renal or adrenal disease, is a constant feature of this syndrome[5]. In the patient described above, large quantities of sodium and chloride were repeatedly present in the urine in the presence of coexistent hyponatremia. For example, on 8-30-66 his urine contained 199 mEq/L of sodium at a time when the serum sodium concentration was depressed. The pathophysiology of the increased sodium wasting which characterizes the syndrome of "inappropriate" antidiuretic hormone production has been the subject of numerous investigations.

Leaf and his co-workers[9] demonstrated that the administration of vasopressin and water to normal volunteers led to the development of hyponatremia followed by an increased renal sodium loss. During these experiments there was an increase in glomerular filtration rate and in renal sodium excretion, and the sodium balance became negative despite a diet containing an adequate salt content. When the fluid intake of the subject was restricted sufficiently to prevent a gain in weight, sodium excretion was not increased, indicating that antidiuretic hormone *per se* did not cause the naturesis. This suggests that the increased renal sodium loss was in some way related to an expansion of the extracellular volume.

There is good evidence that excessive salt wasting is indeed a consequence of overfilling of the extracellular compartment. At least two mechanisms may be operable. Bartter et al.[10] have shown that when the extracellular fluid volume is expanded by the administration of vasopressin and water, urinary aldosterone excretion is decreased. The naturesis can therefore be attributed, in part at least, to diminished aldosterone production. In these studies, as in the studies of Leaf et al.[9], the naturesis and decreased aldosterone excretion which occurred in response to the administration of pitressin and water could be reversed by water restriction. However, measurements of aldosterone secretion and excretion in patients with hyponatremia due to "inappropriate" antidiuretic hormone production have been within the usual range,[5,11] indicating that a decreased aldosterone secretion may not play a major role in the development of the naturesis.

A Hormone

Over-expansion of the extracellular compartment may induce sodium diuresis via a second mechanism. A hormone, as yet incompletely identified, that inhibits proximal tubular sodium reabsorption has recently been recognized. This hormone, the so-called "third factor," is apparently released from the cen-

tral nervous system upon expansion of the extracellular space and, through mechanisms unrelated to aldosterone suppression, causes naturesis[12]. An impressive body of experimental data has been accumulated that indicates this "third factor" to be responsible for the development of the naturesis seen during acute expansion of the extracellular compartment that occurs despite the administration of large amounts of a salt-retaining steroid[13,14,15]. This effect can be reversed by partial clamping of the vena cava[16]. These data suggest the existence of intravascular stretch receptors, located within the thorax, which are sensitive to changes in filling and are concerned with the release of the naturetic hormone. Heinemann and Laragh[17] have described a patient with the syndrome of inappropriate antidiuretic hormone release, in whom the naturesis was abolished by spontaneous occlusion of the vena cava. This observation would support the hypothesis that the naturetic hormone contributes importantly to the salt loss.

Expanded Extracellular Volume

Goldberg[18] has recently reviewed the problem of hyponatremia associated with increased antidiuretic hormone production and has concluded that the naturesis is a result, solely, of an expanded extracellular volume. He suggests that this response serves the useful function of preventing an even greater over-expansion of the extracellular compartment. Thus the relative constancy of extracellular volume is preserved at the expense of tonicity. Although we are unable to document over-expansion of the extracellular space in our patient, we have assumed it was present and contributed importantly to the development of the naturesis.

Curtailment of Fluid Intake

We have been intrigued by another aspect of this syndrome. Hyponatremia will not develop or, once developed, can be corrected by the curtailment of water intake. The voluntary ingestion of water in excess of total water loss represents, it seems to us, "inappropriate" thirst. The patient was highly intelligent, alert, and without evidence of cerebral dysfunction during the course of this study. Yet his voluntary water intake exceeded his excretory capacity. His thirst was not curtailed despite hyponatremia and, presumably, hypervolemia.

Physiology of Thirst

Relatively little is known about the factors regulating thirst in the human. It has been shown that hyperosmolality and/or hypovolemia cause the sensation of thirst[19]. In these circumstances the blood antidiuretic hormone levels are also elevated as both hypertonicity and hypovolemia result in antidiuretic hormone release[20]. Dryness of the mucous membranes or oral pharynx also produces a sensation of thirst irrespective of the individual's actual need for water[21]. However, each of these factors is associated with an increased thirst. The physiologic mechanisms, if any, that can curtail thirst to below normal levels are unknown.

In man fluid consumption is a habit, conditioned by psychological and social factors, and the excretion of water normally varies with variations in intake. When water losses are increased, thirst increases via the mechanisms noted above. When water losses are less than normal, as in the individual who can excrete only a hypertonic urine, thirst does not seem to decrease proportionately.

Three possible explanations occur. *First,* there are no effective homeostatic mechanisms present which can signal the organism to reduce fluid intake below normal. Such mechanisms may be of no biologic survival value since there are few circumstances where such a feed-back system would be beneficial. *Secondly,* homeostatic mechanisms of this type exist but are overwhelmed by habit, or psychologically-conditioned drinking. There is some experimental evidence that this might be the case. Fitzsimons[22] offered water *ad libitum* to rats whose total water requirement was met by intravenous infusion. The animals decreased, but did not cease their oral ingestion of water; and their total water intake was markedly increased over control values. Similarly, patients on intravenous fluid therapy will continue to drink if given the opportunity —a common cause of the hyponatremia that occurs following surgery. *Thirdly,* the inappropriate thirst of this patient and of others

with similar illnesses, as well as that of the volunteers in Leaf's study[9] who received pitressin and water *ad libitum,* may indicate that an elevated blood antidiuretic hormone concentration, per se, is a thirst-producing stimulus. In these circumstances the organism with hypo-osmolality and hypervolemia has the sensation of thirst, but accompanied by an elevated antidiuretic hormone level. The concentration of antidiuretic hormone in blood may play a significant role in the perception of the thirst stimulus. Which of these mechanisms is operant* in this patient is unknown. The role of antidiuretic hormone in thirst perception is, however, a promising area for subsequent investigation.

Summary

A 62-year-old male patient with bronchogenic carcinoma demonstrated hyponatremia, increased levels of blood antidiuretic hormone, and an "inappropriate" thirst. Analysis of biopsy material indicated the tumor contained 525μU of antidiuretic hormone/mg. of tissue. The blood antidiuretic hormone level and serum sodium concentrations returned to normal when a remission was produced by therapy. Upon relapse, hyponatremia and an elevated blood antidiuretic hormone recurred. Hyponatremia could not have developed, despite increased levels of blood antidiuretic hormone and a persistently hypertonic urine, had the patient appropriately curtailed his voluntary water intake. The possible causes of this "inappropriate" thirst may be due to a number of physiologic factors related to antidiuretic hormone.

*See Test Your Word Score Page 649.

Acknowledgment

The authors wish to thank Dr. George Lukemeyer and Dr. Walter Daly for the opportunity to study this patient and Dr. J. Stanley Battersby who obtained the biopsy material.

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All modern men are descended from wormlike creatures, but it shows more on some people.—Will Cuppy

Talk to a man about himself and he will listen for hours.—Benjamin Disraeli

Mr. President—Your Health*

James Monroe (1758-1831)

Healthwise the childhood and youth of our fifth President, James Monroe, was uneventful until early manhood when, during active military service at Trenton, New Jersey, his physical integrity was suddenly violated by a bullet which crashed into his shoulder and severed an artery. Thanks to immediate first-aid attention and subsequent meticulous care in a convalescent camp he survived and recovered; but the bullet remained ensconced in his shoulder for the rest of his life: a unique memorabile of his Revolutionary War service as a young lieutenant in the Third Virginia Regiment.

As a war veteran in Congress Monroe was often absent due to indisposition history fails to identify, but which may well have been of a gastrointestinal nature, a common enough aftermath of active army service. From this complaint he appears to have recovered later, with his health gradually improving until at age 71 he fell off his horse and sprained a wrist—after which, if not because of which—general physical decline set in until he died at age 73 of chronic bronchitis exacerbated by an acute cold.

His death, like John Adams', occurred on July Fourth, a melancholy but fitting memorial to the independence he had valiantly struggled to achieve for his country.

*With acknowledgment to and quotations from Karl C. Wold, M.D.: Mr. President—How Is Your Health? Bruce Pub., 1948.

Flu in Switzerland in 1918

I remember a day in the summer of 1918 when the epidemic of influenza was at its height. I was in the Swiss Army Medical Corps and had to report at headquarters. When I came to the small city of Porrentruy I found myself all of a sudden in a medieval atmosphere of terror and panic. The first sight was a huge stack of new coffins at the railroad station. In the city the population was in a state of tension and extreme nervousness. Many were weeping in the streets. Some had relatives dying at home, others feared for their own lives. The wildest rumors were circulating and found all-too-credulous ears. Alcoholic drinks were supposed to protect against the disease and people were seen drunk in the streets in the early morning. According to another rumor the workers of the local tobacco factory had been spared and I saw women with huge cigars who had never smoked before. . . . Physicians were scarce; they were sick themselves or in the army, and since I was in the uniform of an army physician I was dragged into dozens of houses and was almost kidnaped, so that I could hardly fulfill my task. People clung to the physicians and expected miracles from them, not realizing how helpless we were. A few months later, on an epidemiological survey I came to an Alpine hut, high up in the mountains, and found all the inhabitants dead. It was a horrible sight, the bodies livid and in the early stages of decomposition. Terrified, my guides muttered, "The Black Death"—which it was clinically if not etiologically.*

*Henry Sigerist, M.D.: Medicine and Human Welfare, 1941.

Forgiveness

God may forgive you your sins, but your nervous system won't.—Alfred Korzybski



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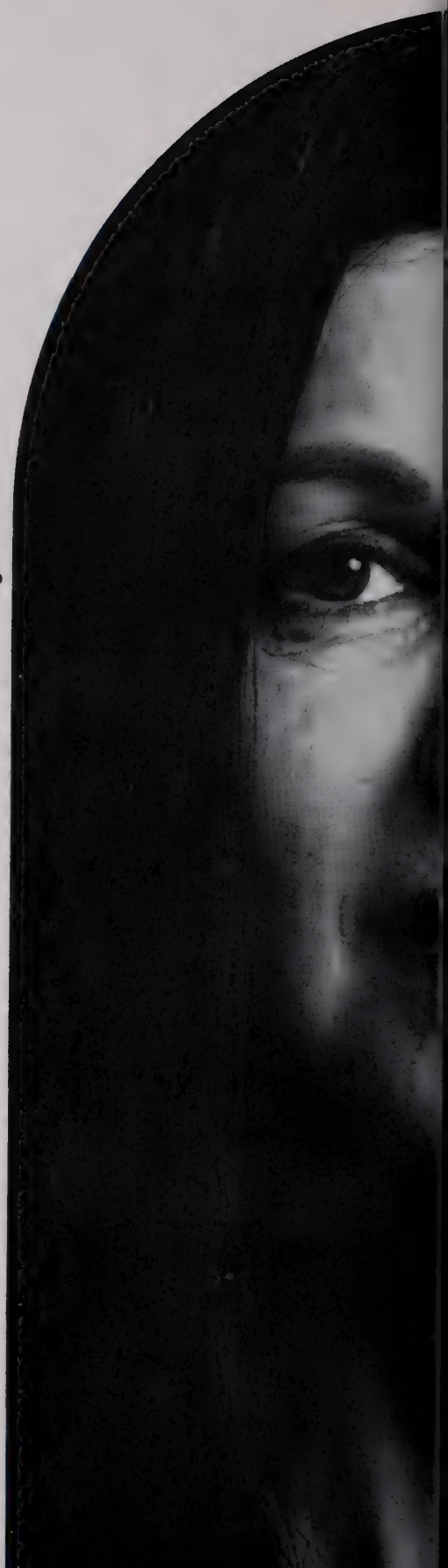
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Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate. Until adequate data are available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.

Precautions: Hydroxyzine may potentiate the action of central nervous system depressants such as narcotics and barbiturates. In conjunctive use, dosage for these drugs should be decreased as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. Hydroxyzine parenteral solution for intramuscular use should be injected well within the body of a relatively large muscle. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. In children, preferably the mid-lateral muscle of the thigh. In infants and small children the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in order to minimize the possibility of damage to the sciatic nerve. The deltoid area should be used only if well developed, such as in certain adults and older children, and only with caution to avoid radial nerve injury. Injections should not be made in the lower and middle thirds of the upper arm. Aspiration should be done to help avoid intravascular injection. On reported intravenous injection a few instances of digital gangrene have occurred distal to the injection site, considered to be due to inadvertent intra-arterial injection or possibly periarterial extravasation. Therefore, particular caution (aspiration and site injection) should be observed to insure injection only into intact veins; avoid either intra-arterial injection or extravasation. Intravenous administration should be accomplished slowly, no faster than 25 mg. per minute, and not to exceed 100 mg. in any single dose. In order to avoid possible adverse effects it is recommended that hydroxyzine parenteral solution be diluted to at least 50 cc. with sterile normal saline and administered over a period of four minutes or more, preferably into the tubing of a running intravenous infusion.

The intravenous administration of this drug is not recommended for children under 12 years of age.

Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.

When this product is given intravenously undiluted, minimal amounts of intravascular hemolysis occur at the site of injection. Giving the maximum recommended intravenous dose (100 mg.) to adults results in immediate transient hemolysis with the liberation of a total of 2-3 grams of hemoglobin, which, in some individuals, can cause small amounts of hemoglobinuria. This compares with the normal red cell destruction from which approximately 8 Gm. of hemoglobin are liberated every 24 hours. If the hydroxyzine is diluted with 50 cc. of normal saline and given during a period of four minutes or more, this phenomenon does not occur.

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More detailed professional information available on request.

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Contraindications: Pregnancy; disease of the central nervous system; evidence or history of blood dyscrasia.

Precaution: Complete blood cell counts should be made before, during and after therapy, especially if a second course is necessary.

Side effects: Infrequent and minor side effects include nausea, metallic taste and furry tongue. Gastrointestinal disturbances, flushing and headache sometimes occur, especially with concomitant ingestion of alcohol. The taste of alcoholic beverages may be altered. Other effects, all reported in an incidence of less than 1 per cent, are diarrhea, dizziness, vaginal dryness and burning, dry mouth, rash, urticaria, gastritis, drowsiness, insomnia, pruritus, sore tongue, darkened urine, anorexia, vomiting, epigastric distress, dysuria, depression, vertigo, incoordination, ataxia, abdominal cramping, constipation, stomatitis, numbness or paresthesia of an extremity, joint pains, confusion, irritability, weakness, cystitis, pelvic pressure, dyspareunia, fever, polyuria, incontinence, decreased libido, nasal congestion, proctitis and pyuria. Elimination of trichomonads may aggravate candidiasis.

Dosage and Administration: In women: one 250-mg. oral tablet three times daily for ten days. A vaginal insert of 500 mg. is available for local therapy when desired. When used, one vaginal insert should be placed high in the vaginal vault each day for ten days; concurrently two oral tablets should be taken daily.

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Dosage Forms: Oral tablets—250 mg.
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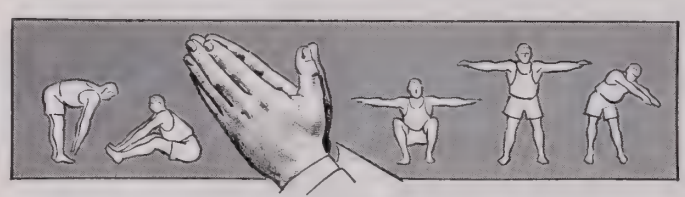
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SOURCE: DUNCAN, G.G.: SCIENCE NEWS LETTER, 83:403 (JUNE 29) 1963.

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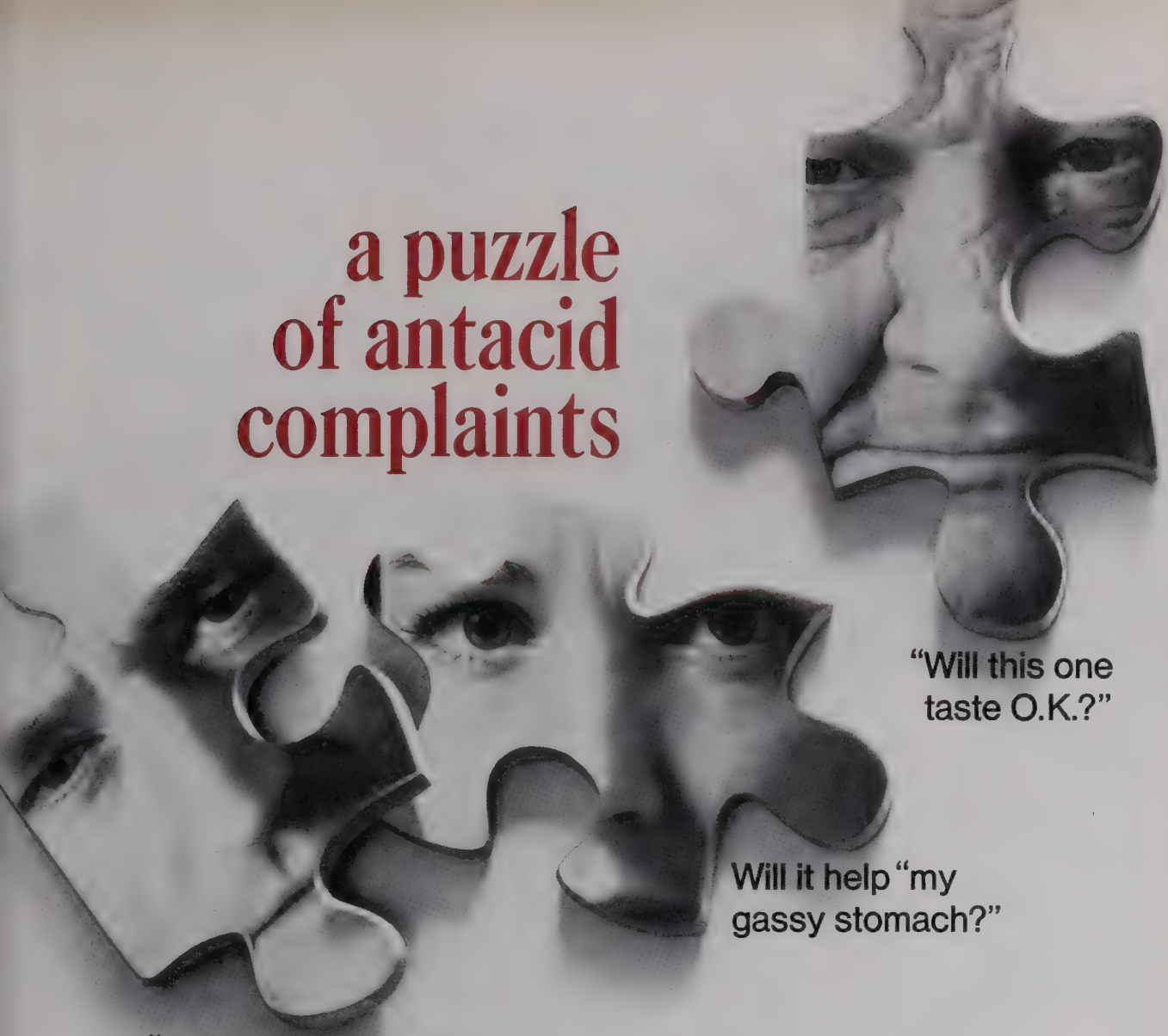
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References: 1. Hoon, J. R.: Arch. Surg. *93*:467 (Sept.) 1966.
2. Danhof, I. E., Personal communication.

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Side Effects: Pseudoparkinsonism and other extrapyramidal disorders are infrequent; drowsiness, especially in high doses early in treatment, may occur; nocturnal confusion, dryness of the mouth, nasal stuffiness, headache, peripheral edema, lactation, galactorrhea, and inhibition of ejaculation are noted on occasion; photosensitivity and other allergic skin reactions may occur but are extremely rare.

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68-114



Editorials

Artificial Heart

In the March issue of Minnesota Medicine* Dr. Blackshear, in an editorial, commented on the international effort to develop an artificial heart and on the approach our group has selected in the development of such a heart. He also made an analysis of the results we have obtained, and his warm endorsements regarding our pump and approach are both gratifying and particularly significant since these views come from a member of a team representing what is commonly recognized to be the heart surgery capital of the world.

In our opinion, the features which distinguish our constrained force-vortex pump from the Telsa pump are responsible in large measure for the capability of our pump to handle the blood atraumatically. Dr. Blackshear made reference to the significant distinguishing feature when he noted that we employed a viscous flow impeller, and then went on to say that the impeller, being remote from the cells, should minimize damage to cells. This is one of the major features that prompted us to select this type of impeller, which we prefer to speak of as a rotator. Using this type of rotator the pressure head and flow are developed by the constrained force-vortex principle in which, after the initial acceleration is imparted by the rotator to the fluid, the fluid itself serves as the prime mover. In contradistinction, the Tesla pump operates as a shear-force pump in which pressure head and flow are developed through the continued action of the impeller as the prime mover due to its closely spaced plates. Although siliconizing the surfaces of our unit helped to keep hemolysis low as pointed out by Blackshear we feel that the engineering features of our pump are of prime importance in avoiding hemolysis.

Approaching the development of an artificial heart by the use of a pump which produces a nonpulsatile flow represents a deviation from the more stereotyped, conventional approaches producing pulsatile flow. The physiological necessity of pulsatile flow has yet to be established.

It will also be important to develop new plastics having stable non-traumatic surfaces. Attention to these and other such basic considerations must comprise an essential part of the program to ultimately develop a successful artificial heart.

The research carried out by Dr. Blackshear's group represents, in our opinion, some of the most scholarly work done in the artificial heart field. Their investigations have been directed at seeking answers to basic and fundamental problems that must be solved in establishing a logically developed mechanical heart program, and their approach should serve as a model for other groups working in this field. It is characterized by a methodical compilation of basic data serving as a solid base from which their overall program may be developed. Great-

*Minnesota Medicine 51:363, 1968.

Weariness "without cause"



Psychic tension with depressive symptomatology?

"For weeks I've done practically nothing and I'm always tired. I wake up tired and I go to bed tired. It's really absurd."

When the patient complains of fatigue, and you can find no organic cause, you recognize that it may serve her as a means of avoiding responsibilities or facing an emotional problem. It is, in effect, a psychological retreat behind a somatic cover of continuous fatigue —one of the many depressive symptoms often associated with psychic tension.

She needs counsel and reassurance, and perhaps a tranquilizer to attenuate excessive tension and help restore the capacity to cope. As an aid to successful management, consider the value of Valium® (diazepam). As psychic tension is eased by Valium therapy, secondary depressive symptoms too may subside. The patient feels more capable, therefore more hopeful; better able to handle situations of intense stress.



Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders; athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindications: Known hypersensitivity to drug; children under 6 months of age; acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in treatment of psychotic patients, and should not be employed in lieu of appropriate treatment. As with most CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increase in dosage of standard anticonvulsant medication; abrupt withdrawal in such cases may also be associated with temporary increase in frequency and/or severity of seizures. Advise patients against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance. Keep addiction-prone individuals (such as drug addicts or alcoholics) under careful surveillance because of their predisposition to habituation and dependence. Use of any drug in pregnancy, lactation or in women of childbearing age requires that potential benefit be weighed against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects —particularly with known compounds which may potentiate action of Valium, such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. Employ usual precautions in the severely depressed or in those with latent depression; suicidal tendencies may be present and protective measures necessary. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation (initially 2 to 2½ mg once or twice daily, increasing gradually as needed or tolerated).

Adverse Reactions: Side effects most commonly reported: drowsiness, fatigue and ataxia. Infrequently encountered: confusion, constipation, depression, diplopia, dysarthria, headache, hypotension, incontinence, jaundice, changes in libido, nausea, changes in salivation, skin rash, slurred speech, tremor, urinary retention, vertigo and blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued. Because of isolated reports of neutropenia and jaundice, periodic blood counts and liver function tests are advisable during long-term therapy. Minor changes in EEG patterns (low-voltage fast activity) observed during and after therapy and are of no known significance.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See **Precautions.**) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

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er emphasis than ever must be placed on injecting similar quality into all research programs, since research spending now involves a very sizable portion of public funds.

Harold D. Kletschka, M.D.*
Edson H. Rafferty, B.S. (Mech. Eng.)*
Houston, Texas

Martin Wynyard, M.D.**
Syracuse, New York

*Veterans Administration Hospital, Houston, Texas.
**Veterans Administration Hospital, Syracuse, New York.

Amputations in Peripheral Vascular Disease

THE SOCIOECONOMIC aspects of peripheral vascular disease* continue to assume increasing proportions in our burgeoning population with greater longevity. Lengthy hospitalizations, frequent complications, demanding nursing care, and poor prognoses in this group of patients in a time of rising hospital costs and tax-supported medical care constitute increasing problems.

Early adequate explanation of the importance of foot hygiene in the diabetic is an oft neglected area of preventive medicine. The proper trimming of toenails and calluses, the protection of corns and bunions, and the early recognition of neurotrophic** disturbances should be promoted. Careful daily bathing, daily changing of socks, and foot inspection are equally valuable for patients suffering from occlusive vascular disease with or without diabetes. In selected patients, sympathectomy may prolong the useful function of the lower extremities. Although arterial bypass procedures have not borne the fruit of promise we had hoped for a decade ago, the indication for their use has been well defined and occasionally is extremely helpful.

The immediate fitting of prostheses has increased the flexibility with which we may deal with amputees, but certain limitations are encountered. The firm confines of the rigid socket on recently wounded tissue whose vascular sustenance is already impaired may lead to occasional wound breakdowns. Open-flap amputations with delayed primary closure, particularly in the face of septic gangrene of the foot, still have a most useful place in amputation surgery.

If we are to deal intelligently and humanely with the patient afflicted by occlusive vascular disease, affording him the best opportunity to find his level of rehabilitation, and if we are to assume our responsibilities in keeping the cost of medical care at an optimal level, a thorough knowledge of the factors affecting amputations is desirable. The comprehensive guide submitted by Dr. Kane offers a succinct summary of our present knowledge.

Ronald L. Linscheid, M.D.
Rochester, Minnesota

*Kane, W. J.: Lower Limb Amputations in Peripheral Vascular Disease: Factors Influencing the Level. Minnesota Med 51:179, 1968.
**See Test Your Word Score Page 649.

Learn to accept in silence the minor aggravations, cultivate the gift of taciturnity, and consume your own smoke with an extra draft of hard work, so that those about you may not be annoyed with the dust and soot of your complaints.

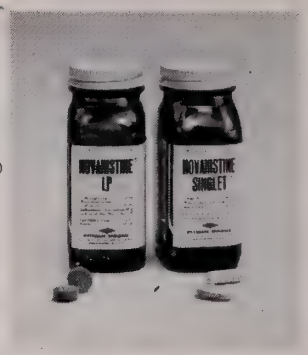
—William Osler

Silence is one of the hardest arguments to refute.—Josh Billings

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Radical Pancreatoduodenectomy

PANCREATODUODENECTOMY is the only treatment that offers any possibility of cure or prolonged survival in relative comfort for those afflicted with cancer of the pancreas, distal common duct, or papilla of Vater.

The operation is an extensive procedure since it involves multiple organs and intricate dissection with multiple suture lines in reconstruction. Mortality and morbidity from the procedure have steadily declined since the operative procedure was conceived over 30 years ago, so that now many medical centers are able to report mortality rates approaching 10 to 15% in the later years of their total experience.

Carcinoma of the pancreas continues to be difficult to diagnose in its early stages. Recent innovations such as celiac angiography and radioactive selenium scan have thus far not been helpful in detecting early lesions. Even at the time of laparotomy, difficulty may be encountered in arriving at a diagnosis, and the surgeon must make a decision based on indirect evidences, the accuracy of which will be influenced largely by his experience in treating pancreatic lesions. Understandably, some surgical departments and hospital staff may insist on a tissue diagnosis before a radical pancreatoduodenectomy is undertaken; but this viewpoint seems to be disappearing, partly because mortality from the procedure has declined, but more especially because multiple negative biopsies do not give absolute assurance that the lesion is benign. Usually this is the case in patients with small lesions having the best chance for cure. This view has been reiterated by so many with extended experiences in pancreatic surgery that it has become common knowledge among our medical colleagues as well as among surgeons at large.

Another area of deliberation is whether a patient with pancreatic carcinoma should have the radical resection or only a shunting procedure? Emphasis has recently been placed on the desirability of taking extra measures to determine if resection is indicated, based upon inspection and the taking of biopsies of various areas outside of the pancreas where early spread is known to occur. Such examination is logical, since extensive procedure should not be undertaken when possibility of cure is remote. On the other hand, something can be said for performing a pancreatoduodenectomy if technically feasible, even though some tumor may be left behind; since large-series reviews show that prolonged and real palliation occurs more frequently in patients who have had resection rather than a bypass procedure.

In reporting results of pancreatoduodenectomy, it is important to differentiate carcinoma of the papilla of Vater from carcinoma of the pancreas since it is well known that the two behave differently. Reports on five-year survivals on the combined groups presents too favorable a view for carcinoma of the pancreas and too unfavorable a view for carcinoma of the papilla of Vater.

The report of L'Esperance* is notable in several aspects. He has shown that radical pancreatoduodenectomy can be done in a relatively small hospital if it is well equipped and staffed. He also has shown that advanced age need not be a deterrent to the extensive procedure and that he has apparently achieved a cure from ductal carcinoma of the pancreas. He further emphasizes that patients should be given every opportunity for cure; and if, at operation, a pancreatic lesion is found but cannot be dealt with for any of a number of reasons other than for advanced state of the disease, surgical assistance should be sought or the patient transferred to a hospital where definitive operation can be done.

Y. Sako, M.D.**
Minneapolis, Minnesota

*L'Esperance, Bernard F.: Radical Pancreatoduodenectomy. Minnesota Med 50:1781, 1967.

**Associate Chief, Surgical Service, Veterans Hospital.

Blame It On Eve

Labor pains are women's penalty for Eve selling apples without a license.
—M. A. Perlstein

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Adverse Reactions: Drowsiness; dry mouth; nasal congestion; constipation; amenorrhea; miosis; mild fever; weight gain; hypotensive effects, sometimes severe with I.M. administration; epinephrine effects may be reversed; dermatological reactions; parkinsonism-like symptoms on high dosages (in rare instances, may persist); lactation and moderate breast engorgement (in females on high dosages); and less frequently, cholestatic jaundice (use cautiously in patients with liver disease). Adverse reactions occurring rarely, include: mydriasis; agranulocytosis; skin pigmentation; epithelial keratopathy; lenticular and corneal deposits (after prolonged substantial doses).

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Diverticulitis

Loffer and Bergquist* call attention to the difficulties encountered in differentiating pelvic masses and tenderness due to diseases of the reproductive organs themselves from those caused by diverticulitis of the sigmoid colon. The case which they report also brings out the possibility that two separate diseases can coexist—in this instance, carcinoma of the endometrium and abscess from a diverticulum of the lower descending colon. While this latter situation is uncommon, the possibility of its occurrence must obviously be borne in mind. One need not go beyond one's own practice to note how frequently it becomes necessary to call in a gynecologic consultant to help in such situations. When fistulae develop, i.e., sigmoido-vesical, sigmoido-vaginal and sigmoido-uterine, the differentiation is greatly simplified. Carcinoma of any of the pelvic organs rarely develops fistulae except in far advanced stages. But simple, tender masses in the adnexae, especially on the left, can frequently cause difficulty.

Diverticulitis of the colon appears to be on the increase. Whether this is due to improved diagnosis or to an increased incidence is difficult to determine. Most authors seem to believe that the apparent increase in frequency has been real. It becomes necessary, then, for us to keep this possibility in mind whenever a patient presents with left lower abdominal pain and change in bowel habits, especially if fever, a sausage-shaped mass in the left lower quadrant and rebound tenderness exist. Symptoms and signs may be much less precise, especially in older age groups where this disease predominates.

Complications which may develop include those mentioned above in addition to free perforation with peritonitis, enterocolic and external fistulae, obstruction and hemorrhage. All but the last mentioned require surgical intervention.

A rather abundant literature concerning medical vs. surgical treatment of acute and recurrent diverticulitis has accumulated, predominantly in the surgical literature. An excellent review of this subject may be found in the British Medical Journal.** These authors concluded, "The course appears more benign than is often suggested, with a strong tendency to natural regression. A few patients experience prolonged and severe morbidity and will merit resection. The study suggests that extension of the scope of resection to include frequent emergency or three-stage resection for patients with acute diverticulitis is not justified."

The decision as to whether surgery should be resorted to after two, three or more recurrences cannot be arrived at by statistical means. It will require the mature judgment of the physician. He will be helped by such considerations as the frequency and severity of attacks, the degree of recovery between attacks, the persistence of a tender mass in the left lower quadrant, persistent fever and leukocytosis, interference with normal bowel function and the like. It is generally agreed that when surgery becomes necessary it should be carried out during a quiescent phase, preferably about six weeks after intensive treatment of an acute attack with bed rest, low-residue diet, non-absorbable sulfonamides and/or appropriate antibiotics and possibly hot abdominal compresses. At that stage a simple resection of the involved segment, making certain that all of the involved colon is included, with end-to-end anastomosis is usually well tolerated.

The subject of bowel hemorrhage from diverticulitis has been well reviewed by Riggs and Ewing.† They believe that *massive* hemorrhage from diverticulitis has been well documented, and that management of this complication should be conservative. However, their review of cases of *mild* rectal bleeding is much more disturbing. In 261 cases of diverticulitis with mild rectal bleeding 50% had associated disease including benign polyp, malignant polyp and carcinoma, with 29% having malignant disease. Careful consideration must, therefore, be given this group and many will require surgery.

R. S. Ylvisaker, M.D.
Minneapolis, Minnesota

*Loffer, F. D. and Bergquist, J. R.: Diverticulitis Complicating the Diagnosis of a Gynecological Malignancy. Minnesota Medicine 50:1793, 1967.

**Bolt, D. E. and Hughes, L. E.: 1:1205, 1966.

†Arch Surg 92:3:321, 1966.



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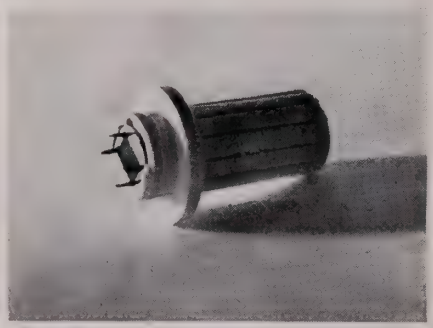
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Laryngectomy

From the time Billroth reported the first laryngectomy in 1873 until Chevalier Jackson outlined indications for the operation in 1904, only a few such cases were reported. In the early years of this century intrinsic laryngeal cancer was treated by thyrotomy without node dissection. Laryngectomy was reserved for advanced laryngeal cancer with removal of cervical lymph nodes, "whether they were felt to be enlarged or not," as advocated by De Santi in 1904.

In subsequent years, with the rise of radium and radiation therapy, extrinsic, i.e., non-cordal, cancer of the larynx came to be considered an inoperable lesion and was widely treated by the newer method. In the last two decades there has been a return to the precepts of the earlier period. Doctors Ogura and Bello in 1955 demonstrated that poorer results in the surgical treatment of non-cordal lesions were due to the presence of microscopic tumor deposits in clinically impalpable cervical lymph nodes. Adoption of routine neck dissection en bloc with laryngectomy has greatly improved cure rates for aryepiglottic fold and pyriform sinus cancers.

Preservation of the voice in the surgical treatment of some supraglottic tumors became feasible as a result of detailed studies of the embryology (Most) and lymphatic drainage (Rouvière) of the larynx. Lymphatic pathways from the supraglottic larynx which develops from the primitive pharynx were found to be independent of those of the vocal cords and subglottic larynx—derived from the superior extremity of the tracheal tube.

Based on these considerations and on the successful two-stage partial horizontal laryngectomy reported by Alonso, Ogura devised a one-stage supraglottic subtotal laryngectomy for epiglottic cancer and reported on its use in 1958. This procedure which preserves both the voice and the swallowing function is a landmark in the surgical treatment of laryngeal cancer. Conservation surgery has since been extended to selected tumors of the pyriform fossa and the posterior pharyngeal wall so that Ogura now feels that as many as half the cases of supraglottic and laryngopharyngeal cancer can be treated with preservation of voice and swallowing.

In the June issue Doctors Ogura and Barnhill* outline their remarkable experience with conservation operations for cancer of the larynx and laryngopharynx. Of particular interest is their success in the surgical treatment of the notorious superior hypopharyngeal tumors with 13 of 32 patients (41%) alive and well at the end of two years, and their restrained optimism in the use of preoperative irradiation for relatively advanced laryngopharyngeal tumors. This last experience concurs with preliminary reports of similar series from Mount Sinai Hospital, New York (Goldman et al.) and Presbyterian-St. Luke's Hospital, Chicago (Hendrickson).

Knowledge of the detailed and precise limits of the tumor in relation to its anatomic site within the larynx is now prerequisite for appropriate surgical attack, and contrast laryngography and cinematography are employed as well as endoscopic methods. A standard classification of laryngeal cancer, such as the tumor node metastasis (TNM) method of staging reported by the American Joint Committee on Cancer Staging and End Result Reporting in 1962, has long been needed for the appraisal of differing therapeutic regimens. In spite of some imperfections pointed out by Norris, this development comes at a time to complement conservation surgery in lending some sophistication to the modern treatment of laryngeal cancer.

John J. Breen, F.R.C.S.
Mt. Sinai Hospital
Minneapolis, Minnesota

*Ogura, Joseph H.: Partial Laryngectomy. Minnesota Med 50:895, 1967.

Speech

He knew the precise psychological moment when to say nothing.—Oscar Wilde



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A Disease Entity?

THE CASE reported by Dr. Mack* in this issue resembles, clinically and pathologically, those cases reported by Reye and collaborators.[1] Unfortunately, Dr. Mack's report does not include any data on the blood or cerebrospinal fluid sugar. The blood urea was not elevated as it had been in nine of the 12 patients reported by Reye and collaborators. The serum carbon dioxide content was normal, whereas it was low in many patients whose cases were reported recently. One could have suspected that this patient had ingested a toxic substance the day he became ill and that this substance caused vomiting. Symptoms and signs of encephalopathy then developed, and autopsy one month later demonstrated fatty changes in the liver and other organs. This pathogenesis could also be proposed in other patients reported to have had Reye's syndrome. In some, an exhaustive search for a toxic agent has been fruitless. It remains to be determined whether or not this syndrome constitutes a clinical pathologic entity with a single etiology. This candid case report illustrates one of the possible dangers of pneumography with the patient under Pentothal anesthesia.

Manuel R. Gomez, M.D.
Rochester, Minnesota

*Mack, R. F.: Encephalopathy and Fatty Degeneration of the Viscera (Reye's Syndrome). Minnesota Med 51:335, 1968.

Reference

1. Reye, R. D., Morgan, G., and Baral, J.: Encephalopathy and Fatty Degeneration of the Viscera: A Disease Entity in Childhood. Lancet 2:749, 1963.

Test Your Word Score

Karyopyknotic—*characterized by shrinkage of nuclei and condensation of chromatin* (page 612)

Aerobic—*growing only in the presence of molecular oxygen* (page 620).

Operant—*operating* (page 629).

Neurotrophic—*pertaining to the nutrition of tissues as regulated by nervous influences* (page 641).

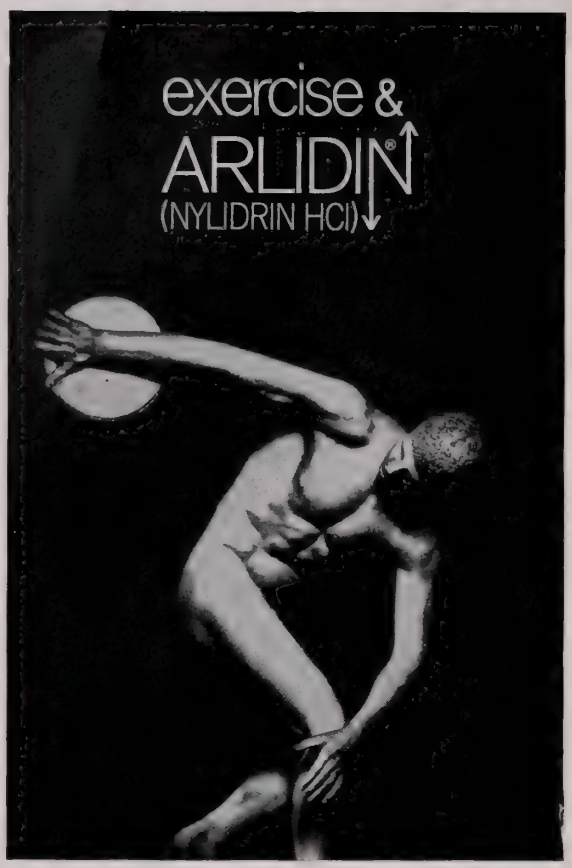
Metachromatically—*staining differently with the same dye* (page 687).

Chylomicra—*particles of emulsified fat found in the blood during the digestion of fat.* (page 690).

Dermatographism—*a condition in which tracings made on the skin leave a distinct reddish, elevated mark* (page 691).

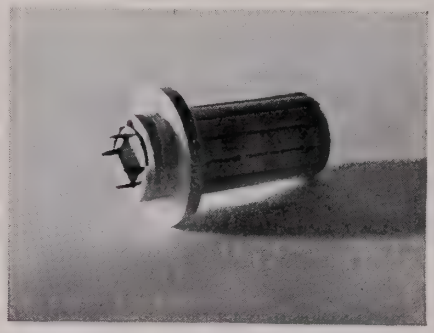
Wilms's tumor—*embryonal carcinosarcoma of the kidney* (page 702).

Anomy—*the state of being without law or order* (page 725).



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The Editor's Soliloquy

That Quintessence of Dust

"The fool hath said in his heart, There is no God" (Psalm 53:1). Likewise the erudite atheist* denies God and disavows a future life. He is convinced there is no hereafter: no immortality of personal selfhood. From his temporal and terrestrial viewpoint, biological man as higher animal shares with the lower animals inevitable annihilation upon physiological death. Supporting his thesis he even quotes Scripture: "Dust thou art, and unto dust shalt thou return" (Genesis 3:19). His conviction is that upon his demise he will become an insensate corpse—doomed to revert to sheer dust. But since the human mind cannot conceive of total extinction of consciousness along with bodily disintegration, the atheist expects to retain just enough of a dim spark of life in his dust to be able to gloat: "See, I told you so! Here I am, a dried-up old corpse, decomposing into a glob of dust—nothing more!"

But from the immurement to which he has consigned himself and through the agency of that same faint but inextinguishable spark may he not have some misgivings when he senses the glorious immortality the rest of us are experiencing—we who scorned to end up as dust and elected to survive? As we enjoy our hereafter in the pursuit of the multitudinous pleasures, experiences and enlightenments which we had to forego during this life because of lack of time, opportunity and sufficient knowledge, may he not perhaps regret that his repudiation of the resurrection was so final and so irrevocable? We shall be experiencing ineffable and transcendent joys in our new dimension while the remains of him lie immobilized and isolated—too deep in the earth to be of any value even to a worm. He cannot join us in our dynamic and radiant self-fulfillment, for sterile static dust cannot enjoy the congeniality of friendship, the thrill to the challenge of sports; cannot appreciate the grandeur of a symphony, enter the absorbing world of generic knowledge or respond to the stimulation of travel throughout the universe.

While he, the non-believer, remains material dust, we, the believers, live a spiritual life beyond the grave. He has proved his point; we have proved ours. To his words from Genesis we have replied with Longfellow's lines: "Dust thou art to dust returnest, Was not spoken of the soul."

And so the ambivalent and cryptic question "And yet to me, what is this quintessence of dust?"** has been answered. To the atheist the quintessence is ALL; to us believers it is NOTHING! He has remained imprisoned in it; we have been released from it.

Carl O. Rice, M.D.

*Atheism is rather in the lip than in the heart—Francis Bacon
**See page 714.

Old Doc Hess says: One of the smug hypocrisies of man is that respectability, which would rather look the other way than cause a fuss. C.O.R.

Surgeons

The best surgeon is he that has been well hacked himself.—Thomas Fuller



Mark Waters was a chain smoker. Wonder who'll get his office?

Too bad about Mark. Kept hearing the same thing everyone does about lung cancer. But, like so many people, he kept right on smoking cigarettes. Must have thought, "been smoking all my life... what good'll it do to stop now?" Fact is, once you've stopped smoking, no matter how long you've smoked, the body begins to reverse the damage done by cigarettes, provided cancer or emphysema have not developed. Next time you reach for a cigarette, think of Mark. Then think of your office —and your home.

American Cancer Society

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MINNESOTA MEDICINE

HONOR AWARD

Minnesota Medicine Medical Writing Awards, 1968

It is the pleasure of the Board of Editors to announce the winners of the seventh annual Minnesota Medicine Medical Writing Awards chosen from articles published in MINNESOTA MEDICINE during the year of 1967.

The first place plaque is to be awarded to W. D. Snively, Jr., M.D. of Evansville, Indiana. His article "Mystery of the Milksick" appeared in the April issue of MINNESOTA MEDICINE, page 469. The presentation will take place during the annual meeting of the Minnesota State Medical Association in Rochester at the New Members, County Officers and Delegates Dinner on Sunday, May 12.

Certificates for excellence in medical writing will be awarded to the authors whose articles were felt to be particularly outstanding by the Board of Editors. These authors are listed on page 657.

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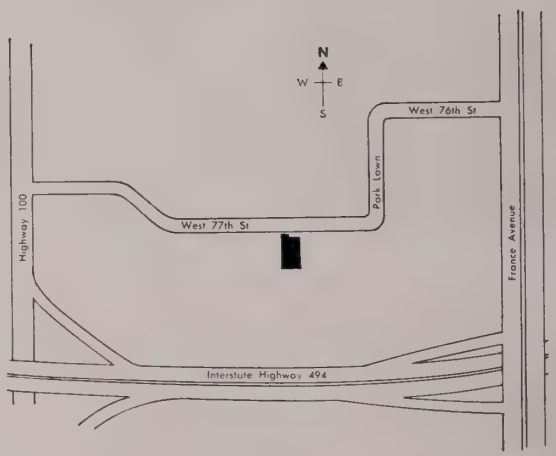
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Sources of sinus headache



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SPHENOID SINUS—most difficult to diagnose. Headache or sense of pressure over vertex. May be pain in ear or mastoid region.



MAXILLARY SINUS—headache and tenderness under eyes at top of cheekbones, usually starting in early afternoon. Possible swelling of cheek. Pain in jaw and back teeth.

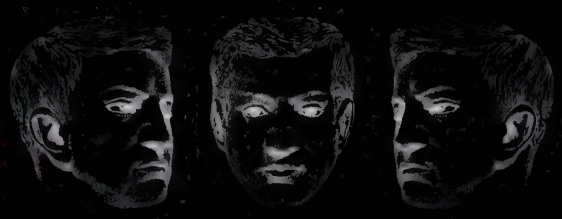
ETHMOID SINUS—headache, tightness in upper part of bridge of nose and well down its sides. Pain, deep-seated behind the eyes and in inner corners of the eyes.



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The MINNESOTA MEDICINE

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Authors	*Manuscript*	*1967 Issue*
Edmund C. Burke, M.D. Rochester, Minnesota	Communication between Parents and Child	December
Roger C. Herdman, M.D. Minneapolis, Minnesota	Generalized Renal Cystic Disease in Children	September
Wilson M. Salter, M.D. and Horace H. Zinneman, M.D. Minneapolis, Minnesota	Bacteremia and Candida Septicemia—Review of 185 Cases during a Four-Year Period	October

Minnesota Medicine is honored to have this opportunity to acknowledge the work of its distinguished authors and to express to them applause, thanks and cordial best wishes.

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Curbstone Consultation

Carpal Tunnel Syndrome

QUESTION: On what basis does one make a diagnosis of carpal tunnel syndrome?

ANSWER: The symptoms related to the carpal tunnel syndrome are due to compression of the median nerve in the carpal tunnel of the wrist. The pain and numbness of the fingers which are noticed in this condition often result in mistaken diagnoses of scalenus anticus syndrome, compression of cervical nerve roots, and other like entities.

The carpal tunnel syndrome may be produced by any condition which restricts the size of the carpal tunnel or changes its contour. The diagnosis is made by demonstrating a positive wrist flexion test, a Tinel's sign over the median nerve at the wrist, and objective sensory findings limited to the median nerve distribution of the hand. Hypesthesia over the median nerve distribution to the hand is the most constant of the clinical findings. Atrophy of the three thenar muscles supplied by the median nerve may result in about half the cases. Surprisingly, there is seldom a history of injury as a cause of this syndrome. Swelling of the flexor synovialis produced by the peripheral vasodilatation that occurs during sleep has been postulated as being responsible for the symptom of "waking numbness" so characteristic of the syndrome.

Injection of a long-acting corticosteroid into the carpal tunnel may serve not only as an excellent diagnostic test, but as an effective method of treatment in this condition.

Harold D. Kletschka, M.D.
Houston, Texas

Invasion of Thoracic Wall

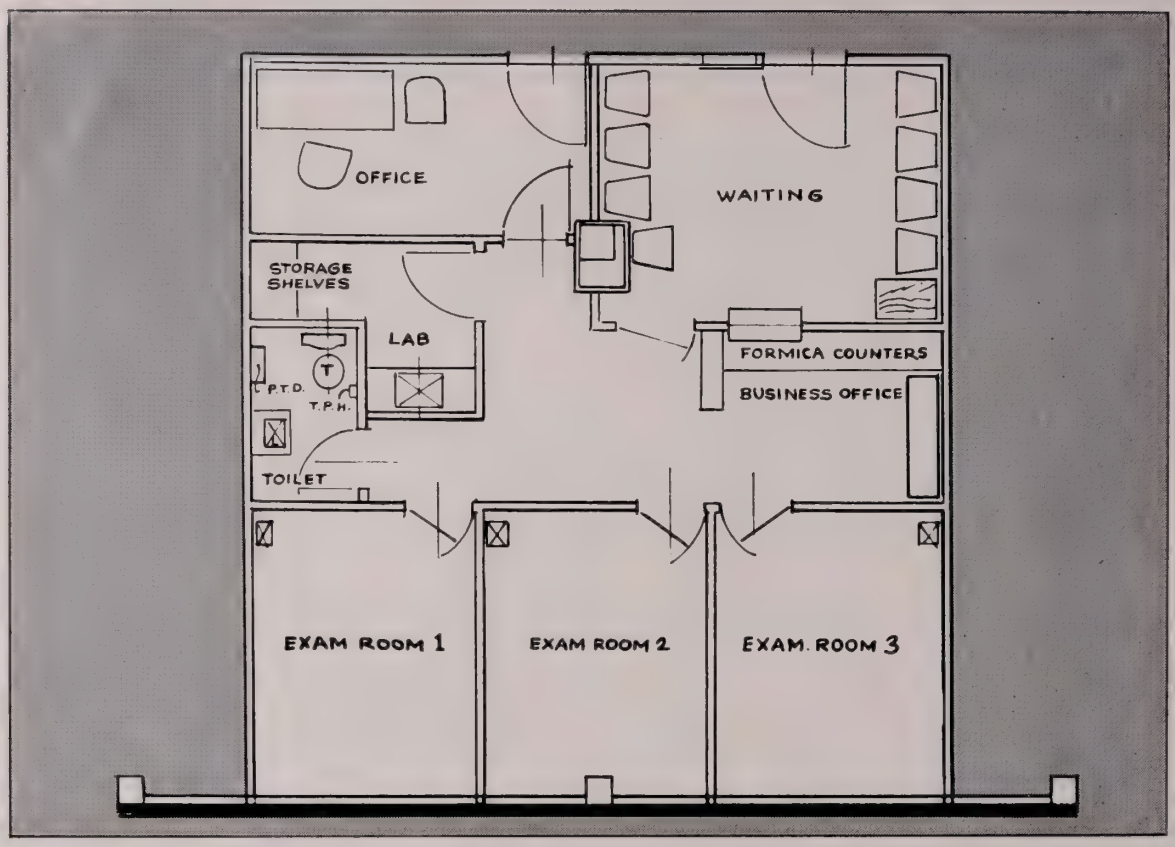
QUESTION: Is invasion of the thoracic wall associated with primary bronchogenic carcinoma a contraindication to surgery?

ANSWER: Perhaps ten percent of patients who undergo surgery for bronchogenic carcinoma will exhibit chest-wall invasion by tumor. This finding in itself is not a contraindication to surgery. When such cases have been subjected to what the surgeon felt was a curative en-bloc resection, as many as a third of such patients have been reported as surviving five years beyond surgery.

Harold D. Kletschka, M.D.
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The Viewing Box

Hip Pain in a 13-Year-Old Girl

THE FILM is that of a 13-year-old girl who complained of right groin pain of progressively increasing severity for the previous five months. She gave no history of injury.

On physical examination, the right hip was tender to palpation, and she was unable to rotate it externally.

What is your diagnosis? (See below.)



Figure (top) anteroposterior pelvis and (bottom) frog pelvis.

Diagnosis: Slipped upper femoral epiphysis.

The left hip is normal. There is relative radiolucency of bony structures about the right hip, indicating that the patient is experiencing pain in the area and is guarding. The upper margin of the right upper epiphysis is flush with the femoral neck. On the frogged view the edge of the slipped epiphysis can be seen projecting beyond the inferior margin of the right femoral neck.

Slipped upper femoral epiphysis affects adolescents in the 10 to 17-year-old age group, a period of rapid growth and vigorous physical activity. Boys are more frequently involved than girls. There is usually no history of trauma.

The growing epiphyseal plate consists of four distinct layers: (1) resting cells, (2) proliferating cells, (3) hypertrophying cells, and (4) endochondral

ossification (zone of provisional ossification). The line of separation invariably occurs through the layer of hypertrophying cartilage. The intercellular matrix, which is responsible for the strength of the epiphyseal plate, is relatively scanty in this area. This is in contrast to the first and second layers where the matrix is abundant.

The exact cause of slipped upper femoral epiphysis is unknown. However, a hormone imbalance has been postulated. It is known that pituitary growth hormone will stimulate the proliferation of cartilage cells, while sex hormone will inhibit growth hormone and decrease the thickness of the epiphyseal plate. Slipping of the upper femoral epiphysis is felt to occur during a period in which exist excess amounts of growth hormone in relation to sex hormone.

In support of this theory, two body types are known to occur frequently among these patients: (1) Fröhlich's type of obesity (decreased sex hormone), and (2) the tall slender rapidly growing individual (increased growth hormone).

The attachment of the epiphysis is quite precarious during this period of growth, being weaker than bone, ligaments, tendons, and the fibrous joint capsule. In view of this, it is surprising that slipped epiphyses are not more common. The answer probably lies in the fact that only shearing forces are capable of producing epiphyseal slippage. The upper femoral epiphysis is the only one in the body normally subjected to shearing forces. Other diseases that predispose to epiphyseal separation are scurvy, rickets, and osteomyelitis.

When the epiphysis slips, it displaces posteriorly and inferiorly, while the femoral neck shifts upward and rotates outward. This results in varus deformity, adduction, and external rotation. The space produced between epiphysis and femoral neck eventually becomes filled with fibrous tissue, callus and cartilage. After a period of time the junction heals. If marked displacement is allowed to persist, degenerative changes become superimposed because of alteration of weight-bearing surfaces.

Clinical symptoms include groin discomfort and slight stiffness in early stages. As the degree of slip increases, pain and limp increase and limitation of internal rotation and adduction appear. If healing occurs with a displaced epiphysis, pain and spasm disappear but limp and varus deformity persist.

Roentgenologic findings in the earliest stage include swelling of the joint capsule, irregular widening of the epiphyseal line, and decalcification of the epiphyseal border of the metaphysis.

As displacement progresses, the head slips inferiorly and posteriorly. Normally the epiphysis extends a little above the superior border of the femoral neck. Minimal degrees of slipping can be detected by the upper border of the epiphysis becoming flush with the border of the neck. The continuity of Shenton's line is broken. The upper border of the femoral neck becomes smoothed off. Callus eventually fills in the space between head and neck.

Treatment begins with immediate cessation of all weight bearing. Most authorities feel that surgery in indicated as soon as the diagnosis is made. If the degree of slip is mild, fixation is accomplished by the insertion of pins without opening the joint. If the displacement is severe, the joint must be opened and the slip reduced before fixation.

Prognosis is excellent if fixation can be accomplished without manipulation or opening the joint capsule. As the extent of surgery increases, the risk of disruption of the blood supply with subsequent avascular necrosis likewise increases.

Fredrick Ekberg, M.D.*
Minneapolis, Minnesota

*Resident in Radiology, Veterans Administration Hospital.

References can be obtained from the author.

Grateful acknowledgement is made to Dr. D. E. Perkins, Alexandria Clinic, Alexandria, Minnesota.



Fracture Conference

Acromioclavicular Separations

Dr. Einer Johnson:*

For the last half of our conference we will discuss the problem of acromioclavicular separation. We will first present six cases to illustrate the problem and the various forms of treatment and then follow with a discussion of the entire problem.

Report of Cases

Dr. Allen Schlein:**

Repair of Ligaments and Transfixion

The first case is that of a 26-year-old white male schoolteacher who had been in a single-car accident on September 27, 1959. The car had rolled over, and the patient's right

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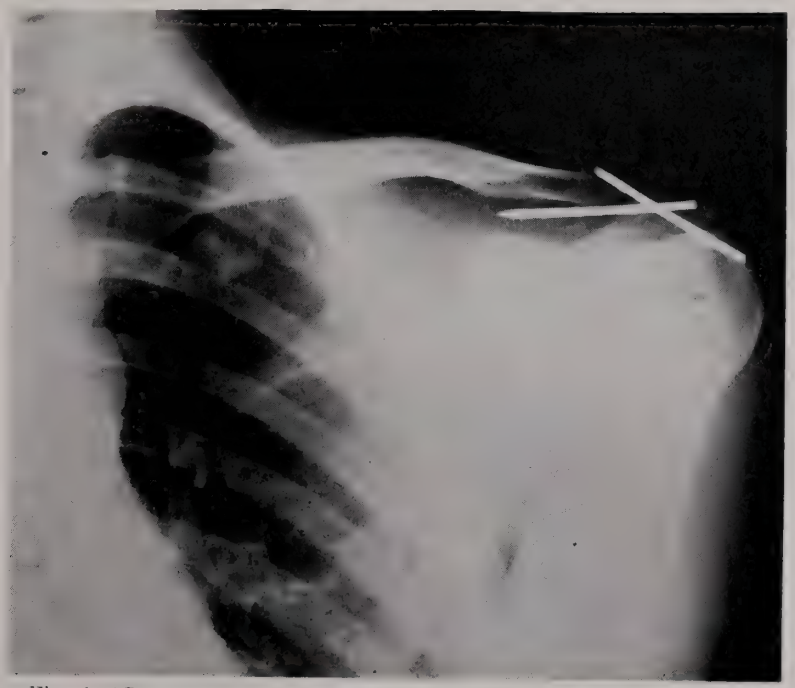


Fig. 1 (Case 1). Roentgenogram taken October 13, 1959, showing reduction of the acromioclavicular separation with two Kirschner wires.

arm had been caught outside the door and pinned to the ground. At the time of admission to the emergency room, he was noted to have a prominence of his distal left clavicle, which disappeared as he became recumbent. The diagnosis of acute left acromioclavicular dislocation was made. On October 5, 1959, an operative reduction was performed in which two threaded Kirschner wires were placed across the left acromioclavicular joint (Figure 1), and tears in the joint capsule and the trapezius muscle were repaired. The coracoclavicular ligaments were considered intact. A Valpeau dressing was applied postoperatively. The Kirschner wires were removed under local anesthesia on December 3, 1959. When the patient was last seen, on April 16, 1960, he was noted to have a slight prominence of the outer clavicle and grade 2 laxity of the acromioclavicular joint. He said he had no symptoms; he had a full range of motion.

Dr. Johnson:

This case is an example of acute acromioclavicular separation in which repair of the acromioclavicular ligaments plus transfixion with two threaded Kirschner wires was carried out. Note that the trapezius attachment was also torn and was repaired at the time of operation.

Dr. Schlein:

Hanging Cast and Pressure

The second case is that of a 16-year-old white boy who had been injured on October 4, 1963, when he had struck his right shoulder on the ground while playing football. On October 11, 1963, stress films revealed a complete acromioclavicular separation (Figure 2), and a closed reduction was performed. A cast was applied from the midpalmar crease to the axilla with the elbow at 90 degrees of flexion. Strips of elastic bandage (Elastoplast) were then placed over the clavicle, extending to the wrist of

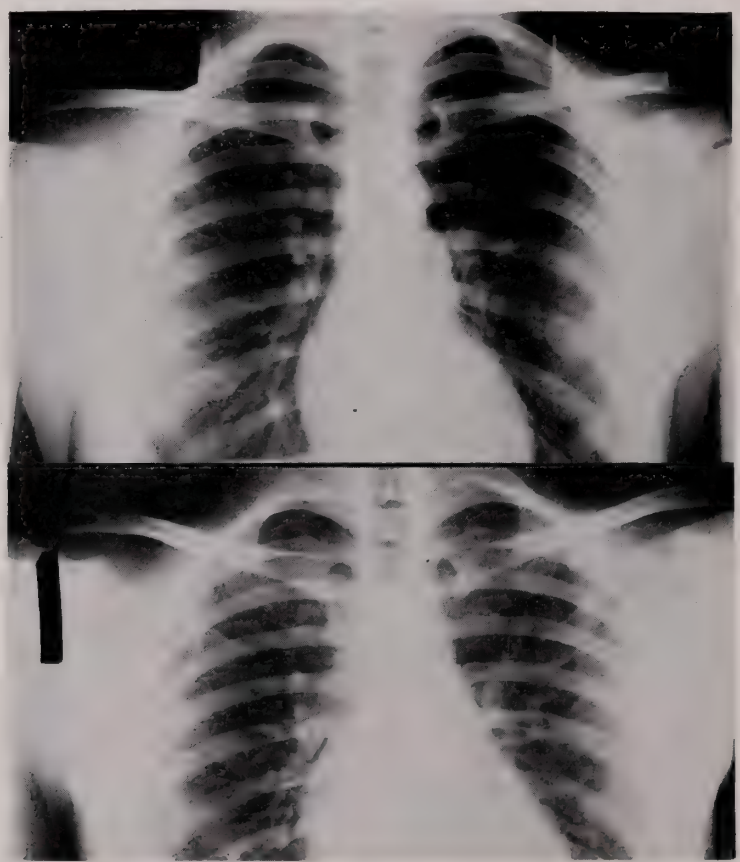


Fig. 2 (Case 2). *Upper,* Stress film taken one week after injury, revealing right-sided acromioclavicular separation. *Lower,* At two weeks after removal of plaster fixation.

the cast; this allowed the cast's weight to depress the outer end of the clavicle. The cast was removed three weeks later. The patient was again seen on November 27, 1963, when he stated that he had been playing volleyball for two weeks and had no complaints. There is no mention in the record of any palpable deformity, and the patient had a full range of motion.

Dr. Johnson:

This case illustrates treatment by closed or nonoperative means. A hanging arm cast was used and pressure was applied across the clavicle by means of a large pad. The cast was suspended from the shoulder in a fashion such that the pad compressed the clavicle, thereby reducing the acromioclavicular dislocation. This illustrates one of the many ways that downward pressure may be exerted on the clavicle by means of a cast.

Dr. Schlein:

Fascial Reconstruction of Coracoclavicular Ligament

The third case involved a 73-year-old white woman who was seen at the Mayo Clinic in June 1967 with the primary complaint of pain in the left shoulder and neck. In 1962 she had fallen on her left shoulder, sustaining a left acromioclavicular separation. Since then she had had progressively increasing pain and had noted a grating sound as her "shoulder" slipped in and out of place. On June 5, 1967, she underwent open reduction of her left acromioclavicular joint. Two threaded Kirschner wires were placed across the joint (Figure 3). The coracoclavicular ligaments were reconstructed with a fascia-lata graft. Postoperatively, a sling and swathe were applied. Except for some minor migration of one of the wires, the patient did well until 13 days after the operation, when her temperature suddenly increased to 102 F. Ultimately a diagnosis of infectious hepatitis was made, and she died in hepatic coma on July 29, 1967.

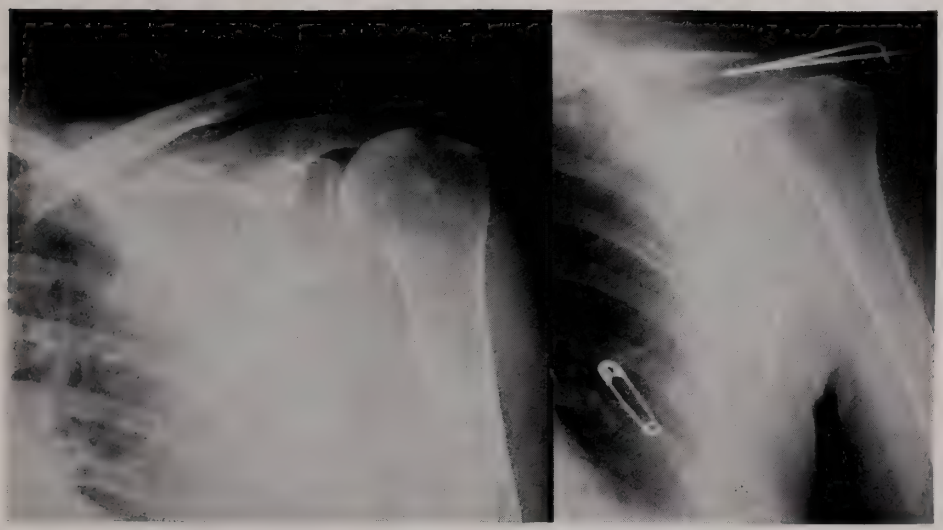


Fig. 3 (Case 3). *Left,* Preoperative roentgenogram showing old dislocation of left acromioclavicular joint. *Right,* Postreduction film, showing placement of two Kirschner wires across left acromioclavicular joint.

In the fourth case, a 65-year-old white man was first seen at this clinic on December 14, 1965, with the primary complaint of left shoulder pain after a car accident. Examination revealed grating of the left acromioclavicular joint and obvious upward displacement of the distal end of the left clavicle. Roentgenograms made while the patient held a 10-pound weight in each hand demonstrated a complete separation of the left acromioclavicular joint (Figure 4). On December 21, 1965, open reduction of the left acromioclavicular joint was performed. Three Kirschner wires were placed across the joint after it had been reduced, and the coracoclavicular ligaments were reconstructed with fascia lata. Postoperatively, a sling and swathe were applied. On February 24, 1966, the Kirschner wires were removed under local anesthesia. At the patient's last

visit, on July 14, 1966, he was noted to be asymptomatic; but his range of motion was five degrees less in all planes on the left compared to the right. At the end of 1967, the patient reported by letter that he was doing well and was completely asymptomatic.

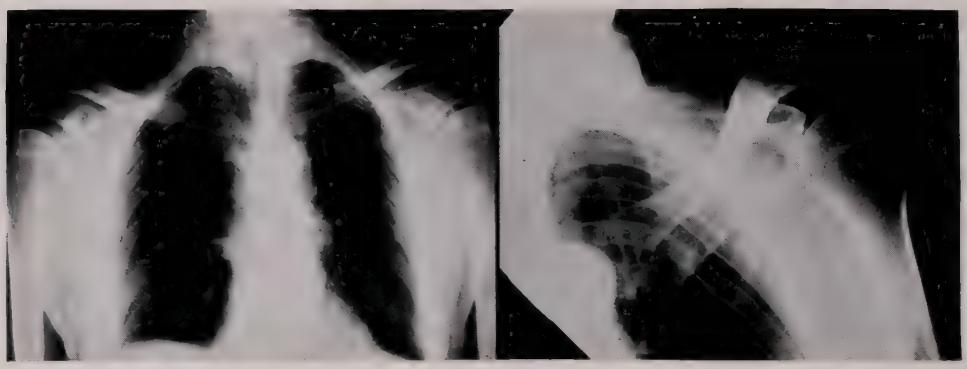


Fig. 4 (Case 4). *Left,* Stress film, revealing dislocated acromioclavicular joint on the left. *Right,* At six weeks after removal of Kirschner wires.

Dr. Johnson:

These last two cases illustrate the use of fascial reconstruction of the coracoclavicular ligaments in a chronic and a complete acromioclavicular separation.

Dr. Schlein:

Excision of Outer End of Clavicle

The fifth case is that of a 39-year-old white male ranch hand who had been thrown from a horse in July 1958. He had landed on his left shoulder and had noted the immediate onset of pain, deformity, and limitation of motion. A sling had been applied by his local physician. His symptoms became progressively worse and he came to this clinic in December 1958 (Figure 5). The distal one inch of the left clavicle was excised and a sling and swathe were applied; shortly thereafter he was dismissed from the hospital. In March 1959 his local physician reported that the patient had returned to heavy ranch work but was somewhat bothered by the deformity of his shoulder.

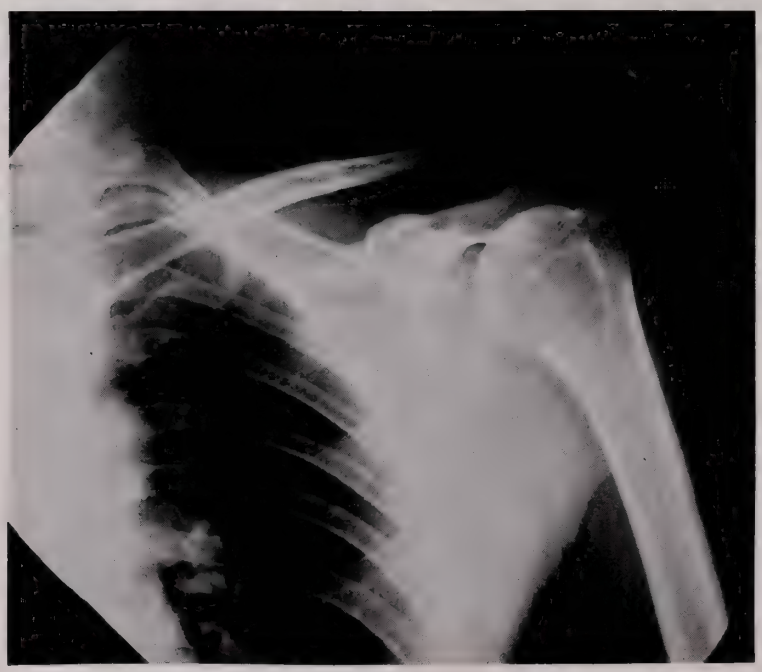


Fig. 5 (Case 5). Preoperative roentgenogram made six months after injury.

Dr. Johnson:

This case illustrates a complete acromioclavicular separation of long duration, which was treated by excision of the outer end of the left clavicle. The patient did not have the weakness of the shoulder which sometimes occurs after this operation, and at the present time he is doing heavy labor without difficulty.

Dr. Schlein:

No Treatment

The sixth case is that of a 24-year-old white man who had been in a car accident on January 23, 1967. In addition to other injuries, he had had an acute left acromioclavicular separation (Figure 6) which had been largely ignored while his more pressing injuries were treated. By December 1967 (11 months after the accident) he had no shoulder symptoms, had ceased to be sensitive about the cosmetic change in the shoulder, and desired no treatment for the now chronic, complete acromioclavicular separation.

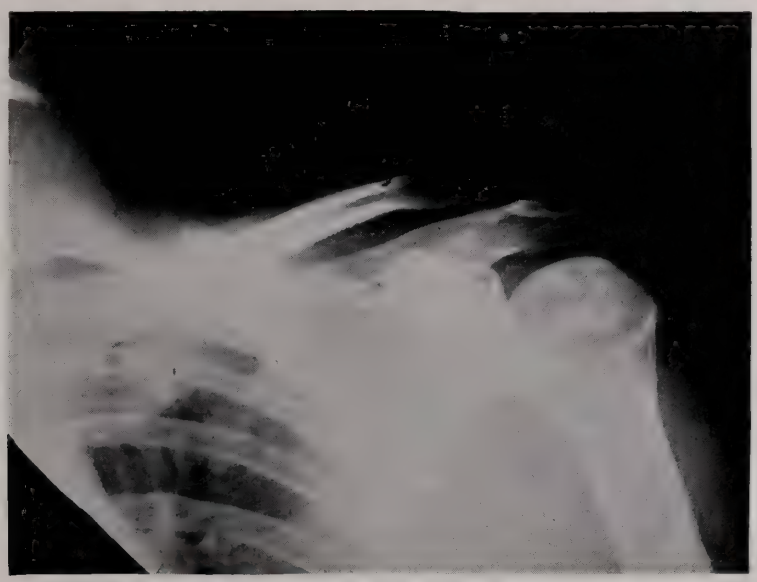


Fig. 6 (Case 6). Dislocation of left acromioclavicular joint.

Dr. Johnson:

Although this patient had symptoms when he was first seen, he ultimately developed full function in the shoulder without weakness or symptoms and elected not to have treatment for his acromioclavicular separation.

Discussion

Dr. Schlein:

The acromioclavicular joint is a small joint of debatable biomechanical importance but of definite literary importance if one considers the amount written on its malfunction. Anatomically it is a synchondrosis containing a small cartilaginous disk and is enclosed by a synovial capsule. A thickened supporting portion of the capsule is known as the acromioclavicular ligament. The structural integrity of the acromioclavicular joint is also somewhat dependent on both the coracoclavicular ligaments and the clavicular attachment of the trapezius and deltoid muscles. However, the acromioclavicular joint may be dislocated completely without any disruption in the integrity of the coracoclavicular syndesmosis.

Complete separation of the acromioclavicular joint occurs in every age group but is commonest in the athletically inclined male between the ages

of 15 and 30 years. The mechanism of injury is a fall or a blow directed over the point of the shoulder, followed by pain, deformity, and limitation of motion.

The typical deformity is comprised of prominence of the clavicle, drop of the shoulder downward and forward, and development of a wide sulcus between the clavicle and the acromion process.

The lesion is usually produced by rupture of the acromioclavicular ligament, perhaps associated with disruption of the coracoclavicular syndesmosis and avulsion of the clavicular attachments of the deltoid and trapezius muscles.

The prereduction roentgenogram usually reveals complete displacement of the articular surfaces of the clavicle and acromion process, increase in the coracoclavicular interval, and downward and forward displacement of the scapula. In some cases, this deformity may be demonstrated only by stress roentgenograms made while the patient is standing upright and holding a 10- or 15-pound weight in each hand. About 5 to 6% of all acromioclavicular separations are complicated by regional fractures.

Conservative Treatment

Most authors agree that subluxation of the acromioclavicular joint does not require surgery, but controversy does exist concerning the treatment of complete dislocation of this joint. Many authors think that the acromioclavicular dislocation can be best treated conservatively. In 1946 Urist stated that 36 methods of conservative therapy had been described in the literature. They included various bandages, adhesive dressings, harnesses and braces, and suspension casts. There are many superficial differences in these appliances but all are designed to depress the clavicle and restore the integrity of the acromioclavicular joint.

Nonsurgical Therapy

The advocates of conservative therapy think that good results can be obtained in 80 to 85% of patients without resorting to a surgical procedure. They also think that surgery has disadvantages in that (1) there will be an operative scar, (2) usually more than one operative procedure may be required, (3) resultant degeneration of the acromioclavicular joint may occur secondary to transfixion, (4) the metallic fixation device may migrate or break, (5) prevention of clavicular rotation sometimes results secondary to lag-screw fixation of the coracoclavicular syndesmosis, (6) there is a possibility of increase in coracoclavicular ligament calcification, and (7) there is a significant incidence of inability to maintain the anatomic reduction after the metallic fixation is removed. The results of conservative therapy of this lesion are difficult to evaluate because of the small size of most published series, such as that of Urist in 1946 and that of Stubbins and McGaw in 1959.

Surgical Therapy

The role of surgical treatment is also somewhat clouded by accounts of more than 30 different surgical procedures in the literature. However, all these procedures are based on acromioclavicular suture, coracoclavicular suture, coracoclavicular fixation, ligamentopexy, or excisional surgery. Two creditable attempts have been made to analyze the results in the various types of surgical procedure. The first, in 1961, was by Lazcano, Anzel, and

Kelly at the Mayo Clinic, and the second was by Wilson of Columbia University and Prothero of North Carolina University at Chapel Hill. Both groups concluded that the greatest number of poor results occurred after metallic fixation of the acromioclavicular joint. It was also noted that the best functional results were obtained after excision of the distal part of the clavicle and the best cosmetic results after coracoclavicular fixation with a lag screw.

In conclusion, we can only state that the large number of methods available for treatment of this lesion indicates there is not as yet a single best method for all patients.

Dr. Johnson:

As suggested by the number of methods of treatment presented in the literature, this is not an easy problem, nor is it one about which there is unanimous thought. Dr. Schlein did not make a point of the difference between acute and chronic acromioclavicular separations, but most writers define the separation as chronic if it has persisted for longer than 14 days. There also seems little doubt that there is both a partial and a complete separation. In partial separation, only the acromioclavicular joint capsule ligaments are ruptured and the clavicle is allowed to elevate up out of the acromioclavicular joint. These patients do not have the marked upward dislocation of the clavicle seen in the complete acromioclavicular separations, but they do have local tenderness over the acromioclavicular joint and will often have a palpable sulcus. The complete acromioclavicular separations are those in which not only the capsule and ligaments rupture but there is also rupture of the conoid and trapezoid portions of the coracoclavicular ligament. This allows the clavicle to ride high with nothing to hold it—no tethering effect by the capsule or the ligaments—and produces a marked upward dislocation of the clavicle, which is obvious on inspection.

By presenting these six cases we have tried to illustrate the various forms of treatment and to give some idea of the results obtained. We did not show a case treated by a lag screw inserted across the coracoclavicular joint. This is surely an acceptable method but one which is not technically easy. The lag screw should be removed after healing of the coracoclavicular ligaments, in six to nine months.

There is no one successful way to treat this problem, and the method chosen by any one physician often depends on his previous experience. If I were to see an acromioclavicular separation in a young athlete, I would surely try to treat it conservatively by some mechanism which produces downward pressure on the clavicle, in the hope of being able not only to gain reduction of the dislocation but to maintain it long enough for the ligaments to heal. However, if I were unsuccessful in this, I would not hesitate to do a fascial reconstruction of the coracoclavicular ligaments. Although there are many other ways of treating acromioclavicular separations, these have been the methods that have served me best. Dr. Kelly, you have written a paper on this problem; what are your thoughts?

Dr. P. J. Kelly:

I agree with you as far as your classification of these injuries is concerned, but I would add a third class in which there is not only complete

rupture of the coracoclavicular ligaments and capsule about the acromioclavicular joint but also avulsion of the deltoid and trapezius muscle insertions. This, I believe, is the third stage of this injury. It is the most severe form and presents the most serious challenge to treatment. When we reviewed the cases at the Mayo Clinic, we found that this problem did not have an easy solution and the treatment for an individual case was almost always dependent on the past experience of the orthopedic consultant in charge.

Dr. M. B. Coventry:

The manner in which this problem has been presented makes it seem simple and easy to determine whether the dislocation of the acromioclavicular joint that has occurred is complete or partial. But making this determination has not always been easy for me. Those cases in which there is only partial rupture of the acromioclavicular joint are much easier to treat, and the success rate is much higher. When one reviews the literature, he is not always able to tell whether the author of the article has made this distinction between complete and partial dislocations, and I sometimes wonder if the end results have not been confused for this reason. I would urge that the physician try to make the differential diagnosis between complete and partial dislocations, because the prognosis for one is a good deal different from that for the other.

Dr. Johnson:

In summary, let me say that this is not an easy problem and the results of treatment are not always satisfactory but are entirely dependent on the extent of the damage which occurs at the time of the injury.

Einer W. Johnson, Jr., M.D.*
Allen P. Schlein, M.D.*
Rochester, Minnesota

*Mayo Clinic and Mayo Foundation.

Low Status of 16th Century Medicine

Now-a-days it is apparent to see how Tinkers, Tooth-drawers, Pedlars, Ostlers, Carters, Porters, Horse-gelders and Horse-leeches, Idiots, Apple-squires, Broommen, Bawds, Witches, Conjurers, Soothesayers, and Sow-gelders, Rogues, Ratcatchers, Runagates and Proctors of Spittle houses with such other like rotten and stinking weeds which do in Town and country, without order, honesty or skill, daily abuse both physic and surgery, having no more perseverance, reason or knowledge in this art than hath a goose, and most commonly useth one remedy for all diseases and one way of curing to all persons both old and young, men, women and children which is as possible to be performed or to be true as for a shoe-maker with one last to make a shoe to fit for every man's foot and this is one principal cause that so many perish.—William Clowes

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Experience is good medicine, but it is never taken until the sickness is over.
—German proverb

Dermatology

Poison Ivy

(Rhus Dermatitis)

RHUS DERMATITIS is the most common contact dermatitis in the United States. This group of plants accounts for as much allergic contact dermatitis as all other contactants combined. Four main groups of plants are responsible: common poison ivy (Rhus radicans) has general distribution throughout the United States; oakleaf poison ivy (Rhus diversiloba) is found in the Southeast; Western poison oak (Rhus toxicodendron) is found on the Pacific coast, and poison sumac (Rhus vernix) is distributed in swampy areas throughout the country. In the Midwest, undoubtedly the majority of cases are due to common poison ivy. These plants may be found anywhere and have even been inadvertently cultivated by gardeners.

A characteristic of this group of plants is that the same sensitizing antigen is common to all. Therefore, cross sensitivity exists among all members of the poison Rhus group and the resulting allergic contact dermatitis is the same. Of interest is the fact that the Rhus group belongs to the same family



Figure

of plants as the Japanese lacquer tree, cashew nut, and mango, to which cross reactions may occur. The common antigenic substance is an oleoresin found in the sap and called urushiol. It is present in the leaves, stems, fruit and roots. Even after the plant is dead this substance may be extracted and has full antigenic properties. Some investigators believe the dermatitis-producing element in this oleoresin to be a pentadecylcatechol (1,2-dihydroxybenzene).

With casual exposure, sensitivity to the Rhus group of plants occurs in 70 percent of the population. If the contact is more prolonged, most individuals would acquire this sensitivity. Susceptibility tends to be greater in fair-complexioned individuals. Patch testing is to be avoided in suspected Rhus allergy, for it may sensitize the individual and is usually not necessary for diagnosis. Clinically, the eruption is very pruritic and is characterized by erythema, edema, papules, vesicles and bullae (Figure). Linear streaking is often present and is of diagnostic help. Usually the eruption appears within one to two days after contact; however, on rare occasions, the onset may be as soon as eight hours or delayed for eight to 10 days. These variances are probably dependent upon susceptibility, extent of exposure and site of contact. The antigen enters within 10 minutes after the oleoresin contacts the skin. Therefore, washing after known or suspected contact with the plant must be prompt if it is to help in preventing the eruption or limiting its severity. Even if this cannot be accomplished, the individual should bathe as soon as possible to remove any residue of the oleoresin. A problem with Rhus oleoresin is that it may contaminate animal fur, clothing and other articles, thereby producing the dermatitis as effectively as if the individual contacted the plant directly. Simple washing with soap or detergents usually removes the oleoresin from these objects.

In the management of mild poison-ivy eruptions one may employ antipruritic shake lotions and oral antihistamines. Topical cortisone sprays can also give relief. Large vesicles may be opened. It is noteworthy that the content of such vesicles is not antigenic and cannot spread the eruption. Colloid baths are helpful and usually welcomed by the patient. If the eruption is more severe with widespread involvement, cool compresses may be used in addition to the treatment already mentioned. At times these eruptions may become generalized and the patient disabled. When this occurs, hospitalization and systemic steroids can aid in hastening recovery.

Prevention of Rhus dermatitis is best achieved by avoidance of contact with the plant. However, in some occupations the risk of contact is high, and in these situations the question of hyposensitization arises. Certain points should be remembered concerning this procedure. First, it does not give complete protection nor is it uniformly successful. Further, it is only temporary and the original sensitivity returns within six months. Another important point to remember is that this procedure must never be used when the patient has active poison-ivy dermatitis, for wide dissemination may ensue. As to date, no topical applications exist which can effectively protect the susceptible individual from this dermatitis. Therefore, recognition of the plant and avoidance remain the ideal prophylaxis.

Willard C. Peterson, Jr., M.D.
Minneapolis, Minnesota

The solar system has no anxiety about its reputation.—Ralph Waldo Emerson

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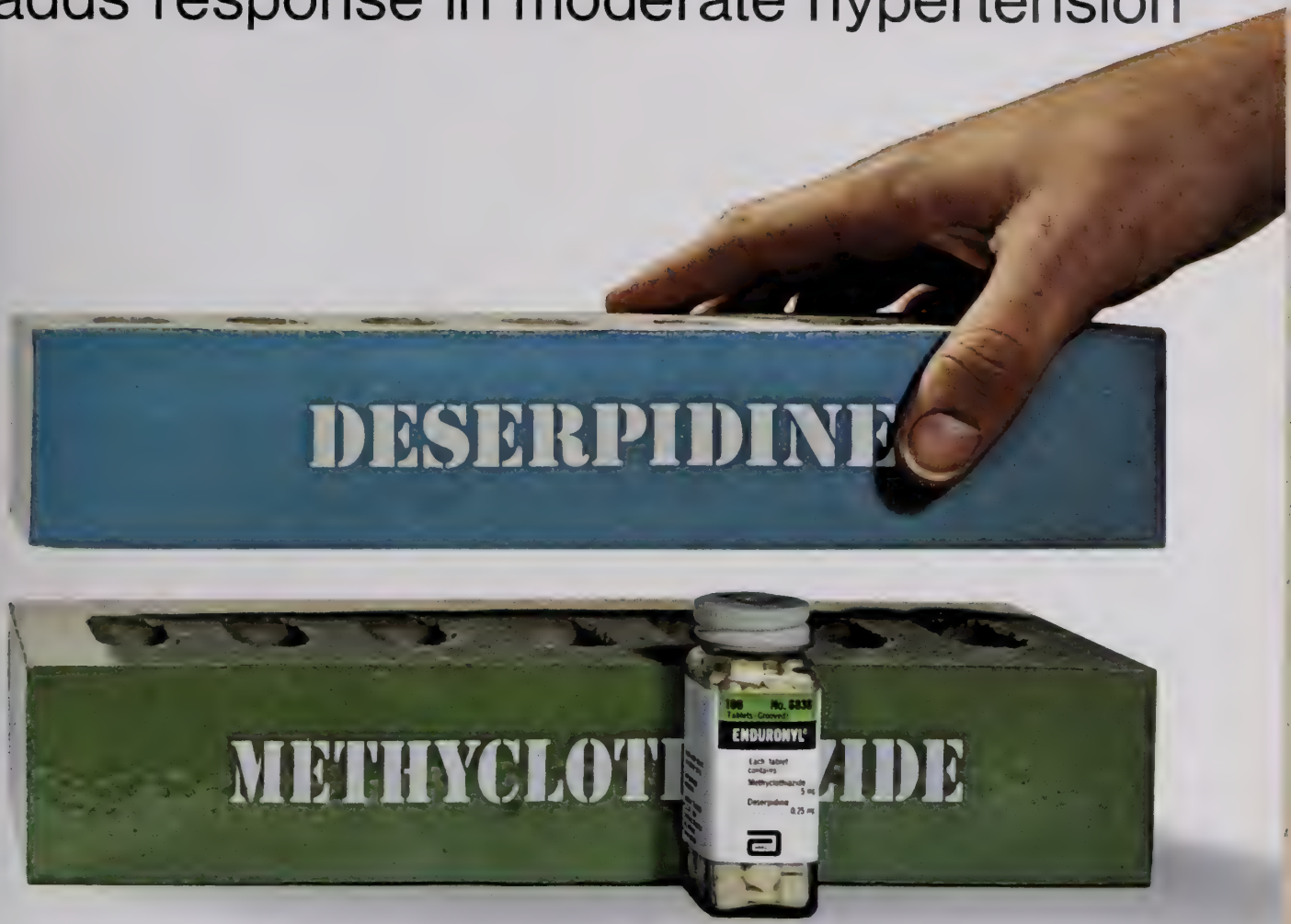
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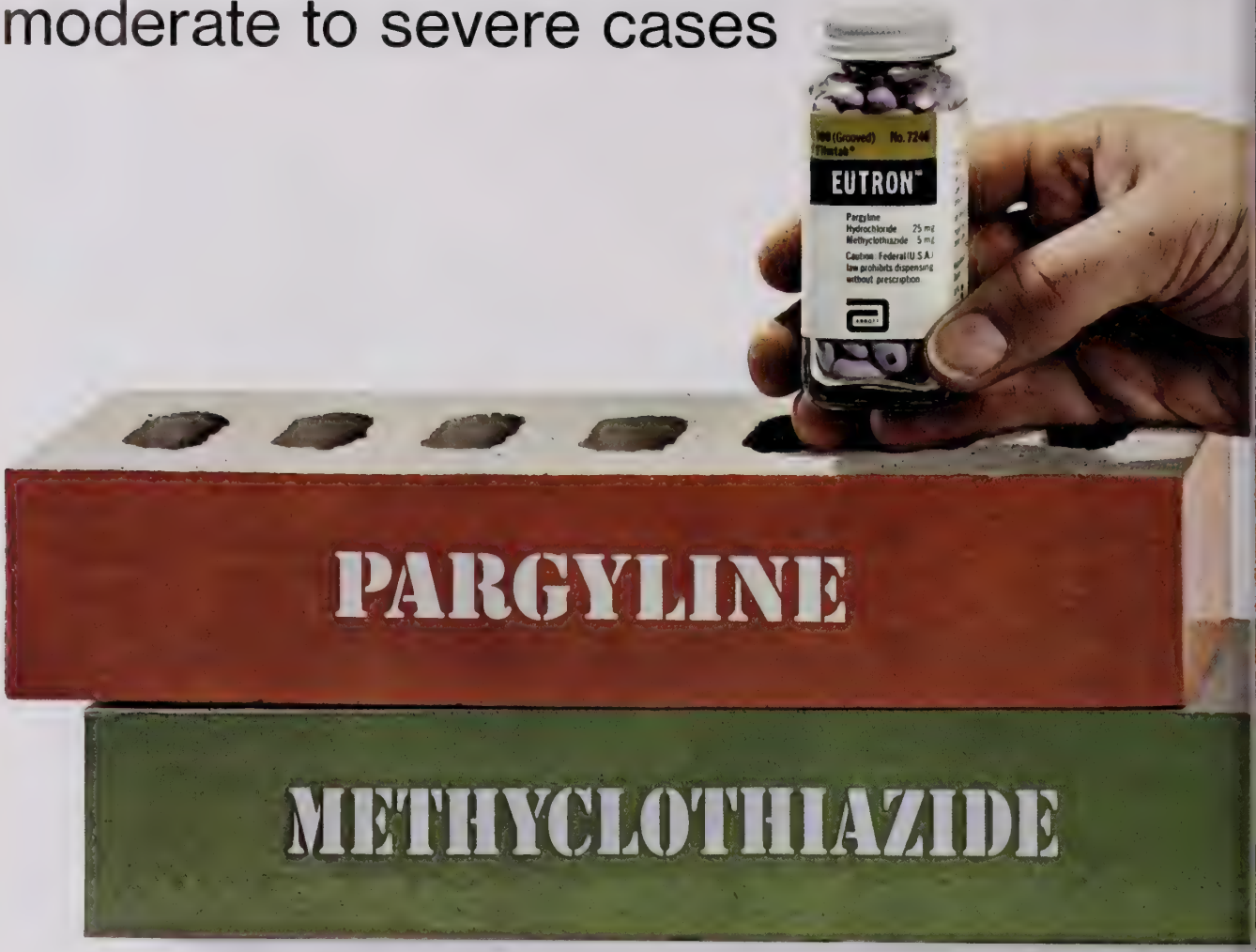
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Contraindications: Sensitivity to thiazides; severe renal disease (except nephrosis) or shutdown; severe hepatic disease or impending hepatic coma (hepatic coma due to hypokalemia has been reported in patients on thiazides). Do not use Enduronyl in severe mental depression, suicidal tendencies, active peptic ulcer, or ulcerative colitis.

Warnings: Consider possible sensitivity where there is history of allergy or asthma. If added potassium is indicated, dietary supplementation is recommended. Reserve enteric-coated potassium tablets for cautious use only when necessary, as they may induce serious or fatal small bowel lesions (stenosis with or without ulceration), cause obstruction, hemorrhage, and perforation often requiring surgery; discontinue them immediately if abdominal pain, distention, nausea, vomiting, or g.i. bleeding occurs. Neither Enduron nor Enduronyl contains added potassium.

Precautions: Use thiazides cautiously in severe renal dysfunction, impaired hepatic function or progressive liver disease; also in pregnancy (bone marrow depression, thrombocytopenia, and altered carbohydrate metabolism have been reported in certain newborn). In surgery, thiazides may reduce response to vasopressors, and increase response to tubocurarine. Antihypertensive response may be enhanced following sympathectomy. Watch for electrolyte imbalance (e.g., hyponatremia) in all patients. In hypokalemia (especially in digitalized patients) give supplemental potassium. In hypochloremic alkalosis, give supplemental chloride.

Use rauwolfias with caution in patients with history of peptic ulcer. Rauwolfias with anesthetics may produce hypotension and bradycardia. Discontinue Enduronyl two weeks before elective surgery. Consider vagal blocking agents during emergency surgery. In epilepsy, adjust anticonvulsant dosage. In electroshock, shorten stimulus strength and duration. In occasional patients with depressive tendencies, rauwolfias may precipitate severe mental depression that usually disappears when drug is stopped.

Adverse Reactions: Thiazide reaction include blood dyscrasias (thrombocytopenia with purpura, agranulocytosis, aplastic anemia); elevation of BUN, serum uric acid or blood sugar; anorexia, nausea, vomiting, diarrhea, headache, dizziness, paresthesia, weakness, skin rash, photosensitivity, jaundice, symtomatic gout, and pancreatitis. Cutaneous vasculitis in the elderly has been reported with other thiazides. Adverse effects with deserpidine are qualitatively similar to those with reserpine, but their incidence is lower. These include nasal stuffiness, abdominal cramps or diarrhea, nausea, headache, weight gain, reduced libido and potency, peptic ulcer aggravation, epistaxis, skin eruption, asthma in susceptible patients, electrolyte imbalance, excessive salivation, and a reversible Parkinson's syndrome. Excessive drowsiness, fatigue, weakness, and nightmares may signal mental depression. Thrombocytopenia, purpura, and a symptom manifested by dull sensorium, deafness, uveitis, glaucoma, and optic atrophy are rare allergic reactions to other rauwolfias. Hypotension from antihypertensive agents may precipitate angina attacks in susceptible individuals. Usually adverse reactions disappear when drug is withdrawn.

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with Methyclothiazide 5 mg.

Indications—Moderate to severe hypertension.

Contraindications—Pheochromocytoma, paranoid schizophrenia, hyperthyroidism and advanced renal failure. Not recommended in malignant hypertension, children under 12, pregnant patients.

Do not use with: centrally or peripherally acting sympathomimetic drugs; foods high in tyramine (e.g., aged and natural cheeses); parenteral reserpine or guanethidine; imipramine, amitriptyline, desipramine, nortriptyline or their analogues; other monoamine oxidase inhibitors; methyldopa or dopamine; separate Eutron and these agents by two weeks.

Sensitivity to thiazides; severe renal disease (except nephrosis) or shutdown; severe hepatic disease; impending hepatic coma from thiazide-induced hypokalemia.

Warnings—Patients: 1. No other drugs (particularly "cold preparations" and antihistamines), cheese or alcohol without physician's consent. 2. Promptly report orthostatic symptoms, severe headache, other unusual symptoms. 3. Angina pectoris or coronary artery disease patients must not increase physical activity with improved anginal symptoms or well-being.

Physicians: 1. Use antihistamines, hypnotics, sedatives, tranquilizers and narcotics (meperidine contraindicated) cautiously in reduced doses. 2. Stop Eutron two or more weeks before elective surgery; in emergency surgery reduce premedication (narcotics, sedatives, analgesics, etc.) to 1/4 to 1/5; carefully adjust anesthetic dosage to patient response. 3. Use cautiously in advanced renal failure. 4. Pargyline may induce hypoglycemia. 5. Consider possible sensitivity reactions when a history of allergy or asthma is present. 6. If potassium is indicated, dietary supplement is recommended; enteric-coated potassium tablets may induce serious or fatal small bowel lesions (stenosis with or without ulceration), cause obstruction, hemorrhage, and perforation frequently requiring surgery; discontinue medication immediately if abdominal pain, distention, nausea, vomiting or gastrointestinal bleeding occurs; Eutron does not contain added potassium. 7. Possible systemic lupus erythematosus has been reported for thiazides.

Precautions—Pargyline: Use cautiously at reduced dosage: caffeine, alcohol, antihistamines, barbiturates, chloral hydrate, other hypnotics, sedatives, tranquilizers, narcotics. Periodically do urinalyses, blood counts, liver function tests, etc. Use with caution in liver disease. Watch for orthostatic hypotension, especially in impaired circulation (e.g., angina pectoris, coronary artery disease, cerebral arteriosclerosis); also, augmented hypotension in concomitant febrile illnesses. Reduce or discontinue if hypotension is severe. In impaired renal function watch for cumulative drug effects, elevated BUN and other evidence of progressive renal failure; withdraw drug if these persist. In surgery increased central depressant response (hypotension and increased sedative effect) can be controlled by (1) discontinuing at least two weeks prior; (2) in emergency surgery lowering dose of premedication; (3) when necessary, administering a vasopressor. Do not use in hyperactive and hyperexcitable patients. Pargyline may unmask severe psychotic symptoms where emotional problems pre-exist. Use cautiously in Parkinsonism, especially with antiparkinsonian agents. In prolonged therapy, examine for change in color perception, visual fields, fundi and visual acuity. Also, prolonged therapy has made certain patients refractory to nerve blocking effects of local anesthetics.

Methyclothiazide: Use cautiously in severe renal dysfunction, impaired hepatic function or progressive liver disease; also in pregnancy (bone marrow depression, thrombocytopenia, and altered carbohydrate metabolism have been reported in certain newborn). In surgery thiazide may reduce vasopressor response and increase tubocurarine response. Antihypertensive response may be enhanced following sympathectomy. Watch for electrolyte imbalance (e.g., hyponatremia). Give supplemental chloride if hypochloremic alkalosis occurs and supplemental potassium if hypokalemia occurs (especially in digitalized patients). Thiazides may decrease serum P.B.I. without signs of thyroid disturbance.

Adverse Reactions — Pargyline: Orthostatic hypotension and associated symptoms, mild constipation, fluid retention, edema, dry mouth, sweating, increased appetite, arthralgia, nausea, vomiting, headache, insomnia, difficult in micturition, nightmares, impotence, delayed ejaculation, rash, purpura, weight gain, hyperexcitability, increased neuromuscular activity and other extrapyramidal symptoms. Drug fever is extremely rare. Reduction in blood sugar and hypoglycemic effects are possible. Congestive heart failure has been reported in a few patients with reduced cardiac reserve.

Methyclothiazide: Blood dyscrasias (thrombocytopenia with purpura, agranulocytosis, aplastic anemia); elevation of BUN, blood sugar or serum uric acid (gout may be induced); anorexia, nausea, vomiting, diarrhea, headache, dizziness, paresthesia, weakness, skin rash, photosensitivity, jaundice and pancreatitis. Cutaneous vasculitis in elderly patients has been reported with other thiazides.

If side effects are severe or persist, reduce dosage or withdraw drug. 804438R

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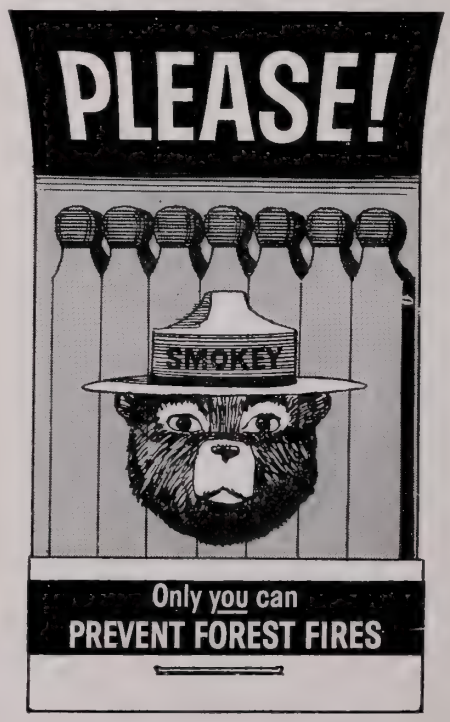


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Tumor Conference

Chondrosarcoma of the Sternum*

TUMORS OF THE thorax comprise about seven to ten percent of all bony tumors in most collected series.[1,3] Primary lesions of the sternum are relatively rare, representing only twelve to twenty percent of this entire group of chest wall tumors. In a survey of 144 tumors of the bony thorax from the Mayo Clinic[4] only 18 were found to involve the sternum primarily. Chondrosarcomas were most commonly encountered, but the other malignant tumors included myeloma, reticulum cell sarcoma, and osteogenic sarcoma. Only one was considered benign and 10 of the 18 patients were dead of the tumor at follow-up. However, only two of the 18 patients had been treated by radical resection.

Presenting Symptoms

Sternal neoplasms most often occur initially with progressive swelling over either the manubrium or sternal area with subsequent development of pain in about one third of the cases. Examination usually discloses a fixed, sometimes tender mass which may be fluctuant. Chest x-rays may indicate localized bony destruction and encroachment of the anterior mediastinal space.

The gross and microscopic features of chondrosarcomas involving the sternum have been thoroughly documented by Dahlin and Henderson.[1] Their course is similar to that of chondrosarcomas in other locations, growing slowly by direct extension and recurring locally if incompletely removed. They also have the potential to metastasize widely, especially in lesions of higher grade malignancy.

Treatment

Principles of treatment depend upon early diagnosis and total excision of the tumor followed by chest wall reconstruction. Although only a few cases have been reported, a high proportion of patients treated in this manner should be salvaged.

The following case report illustrates the problem presented by a large sternal chondrosarcoma and the technique used for its successful removal and chest wall reconstruction.

*Presented at the Minnesota Surgical Society Meeting, Duluth, Minnesota, July, 1967.

Case Report

A 51-year-old woman was admitted to St. Mary's Hospital, Minneapolis, on November 29, 1966, complaining of a painless swelling in the upper sternal area of six months' duration. She also noted generalized weakness, anorexia, mild dyspnea, aching in the right shoulder, and occasional rectal bleeding, all of recent onset. She had spontaneously gained 45 pounds during the previous year. She had a small cystocele and rectocele but otherwise had been in excellent health.

Physical Findings

Physical examination disclosed a well nourished lady in no distress, with normal pulse and blood pressure. There was a 4 x 6-centimeter firm, smooth, slightly tender mass replacing the major portion of the manubrium and the upper sternum and centered more to the right than to the left. There were a few bilateral expiratory rhonchi with deep, rapid respirations; there were normal cardiac sinus rhythm and no murmurs. The right lobe of the liver descended two finger breadths below the right costal margin with deep inspiration and was moderately firm and smooth. Rectal and pelvic examinations were negative.

Laboratory Studies

Routine laboratory studies were within normal limits. Two-hour postprandial blood sugar level was 121 mg. per cent. Other studies, including serum glutamic oxaloacetic transaminase, lactic dehydrogenase, urea and latex agglutination, were negative. Electrocardiograms repeatedly showed abnormal ST depressions in V2, 3 and 4.

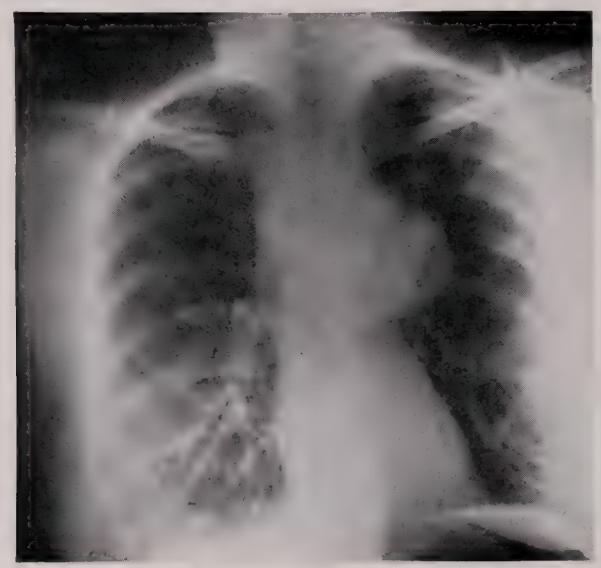


Fig. 1—Posteroanterior chest roentgenogram.

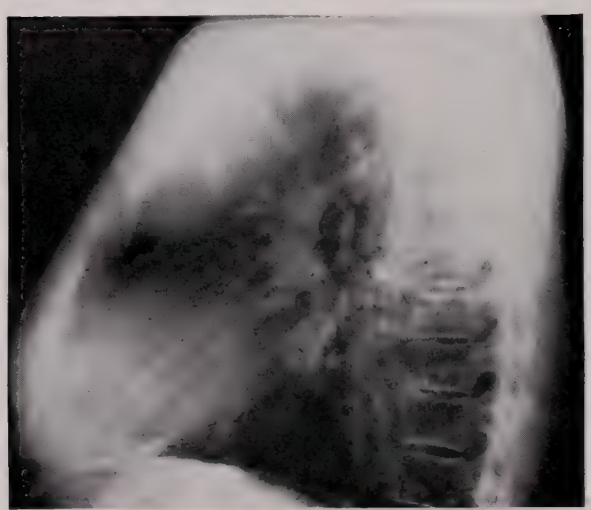


Fig. 2—Right lateral chest roentgenogram.

The posteroanterior chest x-ray (Figure 1) showed a large mass lesion superimposed on the left hilum, and the right lateral view (Figure 2) confirmed its anterior position and demonstrated definite destruction of the upper sternum and manubrium. The remaining lung fields were normal. The cervical spine x-ray showed disc space narrowing at the C3, 4, and 5 levels with associated degenerative changes.

A Silverman needle biopsy, on December 2, 1966, revealed the tumor to be a low-grade chondrosarcoma.

The Operation

Operative removal of the entire tumor was accomplished on December 5, 1966, in the following manner:

The patient was placed in the right lateral decubitus position and a preliminary left thoracotomy performed, widely resecting the seventh rib for future use. The tumor was found to fill the entire retrosternal space but appeared to be quite resectable (Figure 3). The thoracotomy incision was then closed and the patient placed in the supine position. A transverse incision was made over the central portion of the sternum, and large superior and inferior flaps were dissected free superficial to the muscle and facial layers. The pectoral fascia was incised vertically over the lower part of the sternum, and the attachments of the pectoral muscles dissected off laterally over the costal cartilages and ribs as far as necessary to obtain good exposure of the operative area. Superiorly, muscle attachments were sacrificed over the tumor area. The heads of the clavicles were dissected free, and the periosteum was stripped away from the medial 4 or 5 centimeters. The left fourth costal cartilage was then divided and the anterior mediastinal space entered. By working both inferiorly and superiorly,

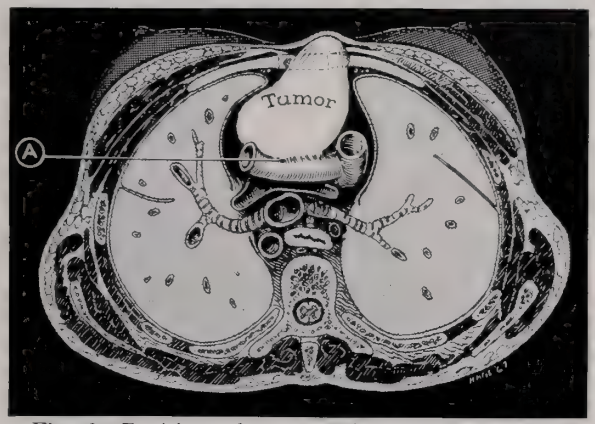


Fig. 3—Position of tumor with attachment to innominate vein (A).

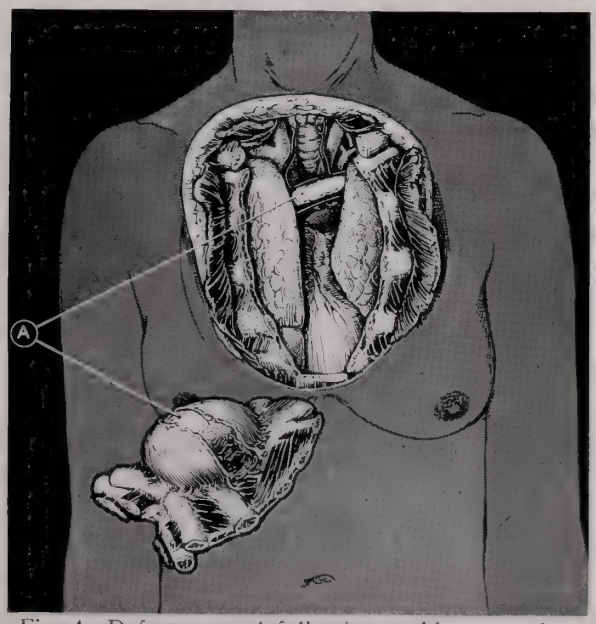


Fig. 4—Defect created following en-bloc resection.

the incision was gradually enlarged by dividing the medial heads of the first, second and third ribs on the left. The left clavicle was then transected 5 centimeters lateral to the costal clavicular junction. Dissection was carried out on the right side exactly as on the left. The internal mammary arteries were ligated. The sternum was divided inferiorly using a Gigli saw just below the fifth costal cartilage. The inferior cut edge of the sternum was elevated, and dissection in the fibroareolar tissue anterior to the pericardium allowed removal of all fatty and nodal tissue. Superiorly, the tumor was dissected off the innominate vein to which it was intimately attached. The internal mammary arteries were ligated at their origin from the subclavian arteries. The right clavicle was transected, and the tumor removed en bloc (Figure 4). The entire defect measured 16 x 14 centimeters. An 18 x 24 centimeter sheet of fascia lata was removed from the left anterolateral thigh through a long vertical incision. Two catheters were placed in each pleural cavity and the fascia sutured in place over the defect under tension. The previously removed rib was placed obliquely across the defect superficial to the fascia lata and wired in place to the left second rib above and the right fourth rib below. After placing bone chips on the surface of the fascia lata, the pectoral muscles were re-approximated in the midline where possible, and the skin and subcutaneous tissues were closed in layers (Figures 5, 6).

Postoperative Course

Postoperatively the patient maintained a satisfactory tidal volume and did not require assistance with her ventilation at any time. Except for temporary urinary retention, her

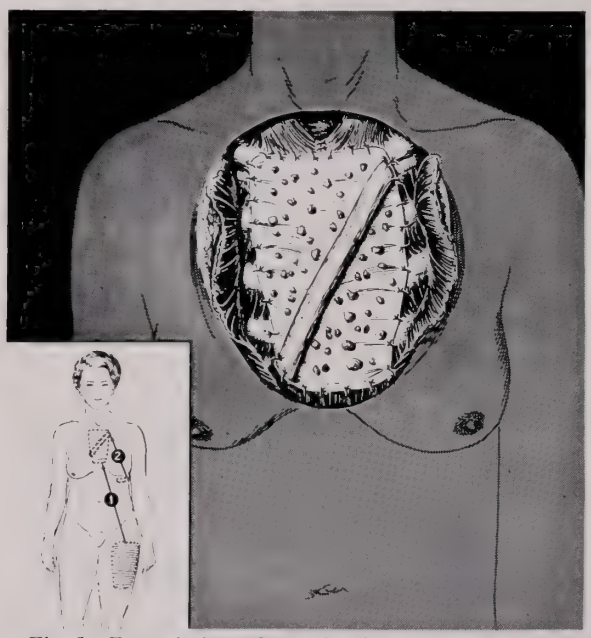


Fig. 5—Frontal view of completed reconstruction.

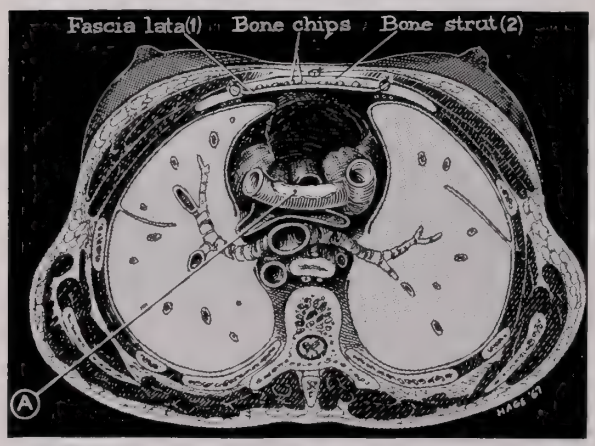


Fig. 6—Cross section illustrating chest wall reconstruction.

postoperative course was uncomplicated, and she was discharged from the hospital on December 16, 1966.

The patient remained in good health but was readmitted to the same hospital on April 3, 1967, for excisional biopsy of a very small nodule in the right breast. This proved to be an adenocarcinoma, and a right modified radical mastectomy was accomplished, sparing the pectoral muscles. The patient was discharged on the fifth postoperative day and has remained well since.

Comment

Most malignant sternal tumors grow relatively slowly and spread by local invasion. This characteristic makes aggressive en-bloc excision the only successful means of primary treatment feasible in the majority of cases. As in the case presented, chest wall reconstruction can be accomplished with relative ease, but it must be tailored to meet the individual requirements of a variety of large defects.

Summary

Primary chondrosarcomas of the sternum invade locally and should be treated by wide en-bloc resection. The extent of chest wall reconstruction depends upon the defect created, often requiring improvised techniques.

Acknowledgment

The authors wish to express deep appreciation to Dr. Thomas J. Kinsella for his advice in this case. His originally described technique of sternal reconstruction (2) was followed closely.

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Louis C. Lick, M.D.
S. R. Maxeiner, Jr., M.D.
Minneapolis, Minnesota

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*James Fisher, M.D.: A Few Buttons Missing, 1951.

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Grand Rounds

Systemic Mast-Cell Disease*

RICHARD R. STURGEON, M.D.
Medical Resident

TISSUE MAST cells were first described in 1877 during an investigation of the staining of fresh tissue by the new aniline dyes then being produced by the German chemical industry. Ehrlich observed that some connective tissue cells contain granules which stain metachromatically** with toluidine blue and other basic dyes. The cells were most numerous in areas of inflammation and near blood vessels. Ehrlich considered these cells to be overnourished connective tissue elements and called them "mast cells."

Mastocytosis, an abnormal proliferation of tissue mast cells, is being recognized with increasing frequency as a systemic disease. This disorder was originally described by Nettleship[1] in 1869 in its cutaneous manifestation, urticaria pigmentosa. Tourraine[2] first reported systemic involvement in 1933. It was not until 1949 that Ellis[3] reported autopsy findings which conclusively demonstrated generalized systemic involvement with infiltrations of skin, liver, bone, spleen, lymph nodes, pancreas and thymus.

An abnormal proliferation of mast cells was found in a patient at Hennepin County General Hospital and stimulated this discussion.

Case Report

The patient was a 71-year-old white male admitted because of an anorexia and weight loss. He was also noted to have rectal bleeding and recent onset of urinary incontinence.

Physical examination revealed a cachectic, dehydrated elderly male. His skin had petechial, non-pruritic, non-blanching brown lesions, maximal over his flanks. Cataracts were present. His abdomen was distended with active bowel sounds. An enema brought

*Presented as a Medical Grand Rounds at Hennepin County General Hospital, November 21, 1967.

**See Test Your Word Score Page 649.

forth bloody mucus. Gastrointestinal workup was negative except for almost no free gastric acid, with persistent filling defect and lack of motility in the cardia of the stomach. Chest and bone x-rays were normal.

A laparotomy was performed and the stomach found to be normal. A slightly enlarged spleen was adherent to adjacent tissue and had many small white and dark nodules over its surface. The liver and the small and large bowel appeared normal. A large number of 1-2 cm. nodules were scattered throughout the mesentery.

On biopsy examination these were lymph nodes and revealed reticulum cell proliferation with increased eosinophils and mast cells. Although there was a difference of opinion, the consensus was that they represented mastocytosis. The bone marrow also demonstrated increased mast cells although peripheral blood was normal.

This patient did not have skin or bone manifestations of mast-cell disease and his scratch test was negative. He had no gastrointestinal symptoms suggesting increased amounts of histamine. In short, he probably had a lymphomatous disease with reactive mast-cell increases.

The patient died but no autopsy was obtained.

Nature of Mast Cells

The mast cell, as defined by Selye[4], is "a connective tissue element which possesses cytoplasmic granules that stain metachromatically under ordinary conditions." The most convincing evidence indicates that these cells arise from small wandering lymphocytes.

It has been shown that wandering lymphocytes take on metachromatic staining in areas of inflammation[5]. Lymphocytes can be stimulated to differentiate into mast cells in tissue culture.

These same authors discussed the relationship of mastocytosis to lymphomatous disease. They stained bone marrow for mast cells in 15 patients with chronic lymphocytic leukemia and found increased numbers of mast cells as well as increased numbers of small lymphocytes. They also noted that miliary tuberculosis and marrow invasion with carcinoma caused lymphocyte and mast-cell proliferation.

Mast cells are found wherever there is connective tissue and are most numerous near small blood vessels. They also accumulate in areas of chronic inflammation, although an infectious etiology has not been demonstrated. Mast cells have been found within a histiocytoma[6], in normal pineal and pituitary glands, and in brain infarcts in the hedgehog[7]. There is also a peculiar localized collection in the thalamus of hedgehogs.

Content of Mast Cells

The function of the mast cell has been inferred from its contents. It has been shown to contain albumin, glycoprotein, polysaccharides, phospholipids[8], mucopolysaccharides[8,9], histamine, possibly serotonin and various enzymes. Enzymes present are: acid and alkaline phosphatase, lipase, stable cytochromicoxidase[8], alkaline protease[9,11] and histadine decarboxylase;[10] but there is no glycogen[8]. The lack of glycogen suggests that the mast cell is a site of active metabolic processes.

Serotonin

Serotonin has been demonstrated to be present in human platelets and chromaffin tissue, but studies on serotonin content in mast cells has led only to confusion. Apparently, mast cells of rodents and dogs contain abundant serotonin, whereas human mast cells contain little or none.

In patients with symptomatic systemic mast-cell disease Ultman[12] has

shown that: (1) serum 5 hydroxytryptamine is too low to be measured; (2) 24-hour urine collections for 5-hydroxyindole acetic acid are within normal limits; (3) tissue levels are within normal limits; (4) tissue 5-hydroxytryptophane decarboxylase is less than in controls.

Occasional reports of elevated urine serotonin products can be explained by disruption of platelets (high serotinin content) secondary to histamine release[13].

Heparin

Heparin has been reported to be the substance which in granules takes metachromatic stain. The mucopolysaccharide in mast cells has been shown to be 80-100% heparin[9], closely related to hyaluronic acid. Mucopolysaccharides isolated from mast-cell neoplasia are heterogeneous, a chondroitin sulfate-like compound[9]. An abnormal mucopolysaccharide has been found in the urine of patients with systemic mast-cell disease[12]. This is apparently unique to this disorder and is a heparitin sulfate. It has no anticoagulant activity and no hyaluronic acid moiety.

It is presumed that heparin liberated from mast cells has little or no local anticoagulant effect and presumably is removed via lymph channels. Also granules (which stain for mucopolysaccharides) are phagocytozed by nearby connective tissue cells, fibroblasts and inflammatory macrophages, and are digested promptly.

Histamine

The presence of histamine is well documented. Riley[8] has shown that tissues containing many mast cells are rich in histamine and vice versa. The injection of "48/80," a potent histamine liberator in the rat, caused not only release of tissue histamine but disruption of mast cells. Certain pathological tissues are extremely rich in histamine and mast cells, e.g., mastocytoma. It is noted that certain fetal tissue is devoid of mast cells and histamine. However, this same tissue in adult animals is rich in both.

Blood levels of histamine in systemic mast-cell disease have been measured and found to be 4.0 ugm/ml, compared to a normal of 0.02-0.08 ugm/ml. Histamine content of spleen was 30 times normal[12]. Spleen and skin homogenates contained increased levels of histadine decarboxylase as well as increased histamine[10]. Transient histaminuria reflects transient histamine release in most diseases. The level in urine is proportional to the blood level. This may be correlated with symptoms as well, but mastocytosis does exist without histaminuria.

The histadine decarboxylase previously mentioned has been found to be five times normal in a spleen invaded with mast cells[13].

The histamine metabolism in systemic mast-cell disease has been studied in an effort to detect a possible metabolic defect.[10] Carbon[14]-labeled histadine injected had a normal disappearance rate; likewise, C-14-labeled histamine was metabolized at a normal rate, negating a degradation block. The most likely possibility is that histamine excess results from simple overproduction of histamine by increased numbers of cells.

What then is the normal function of this cell? Riley[15] has shown that an inflammatory reaction creates an increase in tissue mast cells. He painted the skin of mice with known carcinogen initiators. The inflammatory reac-

tion and dysplastic epidermis was bordered by a layer of mast cells, a response which persisted until dysplastic cells underwent malignant change, at which time the mast-cell response no longer occurred.

Histamine appears to stimulate phagocyte capacity of the reticuloendothelial system and "activates" loose mesenchymal cells.

Mast-Cell Cycle

These phenomena have lead Riley to propose the "Mast Cell Cycle" theory. Trauma and/or acute inflammation causes rupture of mast cells. Fast-acting histamine causes vasodilation and increased permeability with concomitant increase in plasma colloid exudation. Histamine activates connective tissue cells which phagocytose colloids and heparin. Heparin is closely related to hyaluromic acid and these cells are now "full" and primed for metabolic needs in preparing mucopolysaccharides of their own to lay down ground substance.

Function of Mast Cells

Detoxification

This theory has had some doubt shed upon it by the observations of Chayen.[16] Mast cells in tissue culture were noted to swell and become visible in response to histamine. Continued exposure to histamine causes the mast cell to burst, which suggests a detoxification function.

Further findings relate mast cells to the process of necrosis.[17] Mast cells in a test system appeared to have the capacity to increase tissue resistance to necrotizing agents.

Protection by Heparin

It is known that heparin inhibits both normal and malignant cell growth in tissue culture.[5] It has also been shown that rat tumor grows faster in subcutaneous implants if the animal is depleted of mast cells with 48/80.[18] This loss of "protection" was not corrected with histamine, heparin or serotonin. It is interesting to speculate on this potential role of mast cells.

Heparin has known antithromboplastin and antithrombin activity; it also functions in chylomicra* dissolution and fat transport. Swank and Levy[19] injected heparin in dogs and found decreased circulating chylomicra and apparently enhanced chylomicra transport through capillary walls. Bragden[20] showed that antiheparin compounds increased serum lipids.

Change During Hibernation

Evidence is available that mast-cell function is under general body regulation.[5] Hibernating animals are noted to have both increased mast cells and increased clotting times. Thyroid-stimulating hormone is known to increase the number of mast cells, while thyroid hormone has an opposite effect. Both adrenocorticotropin polypeptide and cortisone decrease mast cells and conglomerate their granules.

Clinical Features

Skin

The most obvious lesion in systemic mast-cell disease is urticaria pigmentosa: a dermal infiltration with mast cells, producing red-brown discrete macules mainly over the trunk. The lesions may have a waxy appearance,

*See Test Your Word Score Page 649.

usually persist indefinitely, and are non-pruritic unless they urticate. Urtication is produced by even minor trauma. Two thirds of patients will demonstrate dermatographism.*

The onset of urticaria pigmentosa in childhood has a different prognosis from that of adult onset. Of 28 cases, four have cleared (three in childhood), seven to eight have improved, and the rest are unchanged.[21] Another series[22] of 26 cases in children reported that six cleared, fourteen improved, and two remain unchanged. Generally, cases acquired in late childhood or early adulthood tend to persist.

Mast-cell proliferation can occasionally occur as an isolated lesion, i.e., as mastocytoma, usually 3-4 cm in size.[23]

Systemic Manifestations

Of persistent cases of urticaria pigmentosa, Caplan[2] reports that 15-30% at some time have systemic involvement, and of these lesions, one third become malignant.[23] It is of interest that visceral manifestations of systemic mast-cell disease usually post-date the onset of skin lesions by many years. Enlargement of spleen, liver, and lymph nodes represents early evidence of widespread mast-cell proliferation in the reticuloendothelial system.

The physiologic effects of excess histamine are quite evident in the clinical expression of this disease. Facial flushing, pruritis, tachycardia, headache, malaise, and dermatographism are common. Histamine stimulation of the gastrointestinal tract causes nausea, vomiting, cramps, diarrhea, and peptic ulceration. Acute histamine reactions can be precipitated by exposure to cold, trauma, radiation, infections, alcohol, and/or alkaloids. Some problem in differentiation from carcinoid exists. Generally, carcinoid causes more lower than upper gastrointestinal symptoms. There is more respiratory involvement, i.e., bronchospasm, and it produces an erythema with cyanosis, as contrasted to the bright red flush of histamine.

Visceral Involvement

As viscera become involved, many symptom complexes occur. Migratory bone pain is not uncommon, as bone can be invaded anywhere. Radiologic findings are extremely variable; increased or decreased bone density, increased trabeculations, bone islands, and/or periosteal thickening have all been reported.[25]

Hepatomegaly, splenomegaly, and lymph-node enlargement have been mentioned and reflect mast-cell proliferation. A hematologic dissemination may occur, i.e., mast-cell leukemia,[26] though mast-cell leukemia has been reported without the clinical picture of mast-cell disease.[7] Almost always, however, cutaneous manifestations are present.

Gastrointestinal involvement is reflected by pain, nausea, vomiting, flatulence, and diarrhea. These effects, at least initially, are secondary to histamine and are related to cutaneous flareups. Strangely enough, the expected increase in gastric acidity has not been demonstrated.[22] The reason for this remains unexplained.

Steatorrhea has only rarely been reported. A group from Copenhagen[28] reported steatorrhea and hypocalcemia. They also noted normal villous architecture and crypts on small-bowel biopsy. Mast cells were present in the lamina propria and muscularis. Liver biopsy was normal. On the other hand, a report from South Africa[29] revealed similar steatorrhea and hypo-

*See Test Your Word Score Page 649.

calcemia (even tetany), but jejunal and ileal biopsy demonstrated short, blunt villi. A marked infiltrate with eosinophils was present in the submucosa, with deeper mast cells and inflammatory cells. The blunted villi were presumed to be secondary to eosinophil infiltrate. It has been shown that histamine is chemotoxic to eosinophils and that continued or intermittent exposure can cause an eosinophil response. This patient responded clinically to steroids.

Bleeding Diathesis

A bleeding diathesis is occasionally reported. Efforts to demonstrate increased levels of heparin have been of no avail.

Anemia is often present, and mast cells are abundant in the marrow.

Mast cells are also found in bone, and patients may have low serum calcium and elevated alkaline phosphatase.

Therapy

Isolated reports of brief remissions utilizing steroids exist, as in the case reported from South Africa.[29] However, no case of bona-fide systemic mast-cell disease with tissue diagnosis has shown a prolonged response to steroids.

Occasionally antihistamines will afford some symptomatic relief, but reports of improvement in diarrhea and pruritis are the only consistent findings. The specific anti-serotinin preparation, Periactin, is no better than antihistamines.

Summary

In summary, systemic mast-cell disease usually presents as long-standing urticaria pigmentosa, typically with dermatographism. Migratory bone pain and symptoms of histamine release occur. Gastrointestinal symptoms range from nausea and cramps to steatorrhea. Hepatosplenomegaly and lymph-node enlargement are present, and weight loss may be evident.

Laboratory studies reveal pancytopenia, and occasionally low serum calcium and elevated alkaline phosphatase. Fecal fat may be elevated. Bone lesions may appear.

Though many patients of urticaria pigmentosa go through life without difficulty, when symptoms such as the above appear further studies are indicated. Diagnosis can be made only by tissue examination. Skin, marrow, and lymph-node involvement can be detected with special stains. The pathologist should be forewarned, as mast cells may not be obvious on routine stains.

References may be secured from the Grand Rounds Editor.

Smoking—A Compulsion Neurosis?

Tens of millions of persons smoke. And tens of millions will tell you that they're not men enough, or women enough, to quit. And so, by a process of mathematics, we must accept it as reasonably normal.

If there were only a few thousand smokers unable to quit, then we would call it a compulsive neurosis. By its very nature, a neurosis must be a minority report on the subject of human behavior.*

*James Fisher, M.D.: A Few Buttons Missing, 1951.

If fifty million people say a foolish thing, it is still a foolish thing.—Anatole France

He that is good for making excuses is seldom good for anything else.—Benjamin Franklin

When the talk turns to oral contraceptives, it makes medical sense to remember low-dose Norinyl®-1.

(norethindrone 1mg. & mestranol 0.05mg.)

Turn page for contraindications, precautions and side effects.



Reduction of oral contraceptive dosage to the lowest effective levels is a well-accepted principle of conservative medical practice. In keeping with this view, Norinyl is now also available as Norinyl-1, containing exactly one half the previous dosage of norethindrone and mestranol. Clinical experience has established that effective fertility control can be achieved with the same degree of reliability and safety with new Norinyl-1 when taken as directed.

What about switching patients from higher dosage forms?

In transferring patients to low-dose Norinyl-1 from higher-dosage oral contraceptives, some breakthrough bleeding may occur in the early cycles. In the majority of cases the bleeding episode is mild and self-limited. The long-term advantages of the lower dosage form should be weighed against the inconvenience of possible breakthrough bleeding in the individual patient.

Contraindications: 1. Patients with thrombophlebitis or with a history of thrombophlebitis or pulmonary embolism. 2. Liver dysfunction or disease. 3. Patients with known or suspected carcinoma of the breast or genital organs. 4. Undiagnosed vaginal bleeding.

Warnings: 1. Discontinue medication pending examination if there is sudden partial or complete loss of vision or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn. 2. Since the safety of NORINYL-1 (norethindrone 1 mg. with mestranol 0.05 mg.) in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. 3. Detectable amounts of the active ingredients in oral contraceptives have been identified in the milk of mothers receiving these drugs. The significance of this dose to the infant has not been determined.

Precautions: 1. The pretreatment physical examination should include special reference to breast and pelvic organs, as well as a Papanicolaou smear. 2. Endocrine and possibly liver function tests may be affected by treatment with NORINYL-1. Therefore, if such tests are abnormal in a patient taking NORINYL-1 it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, preexisting uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions that may be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. NORINYL-1 should be used with caution in patients with a history of cerebrovascular accident. 6. In relation to breakthrough bleeding, and as in all cases of irregular bleeding *per vaginam*, nonfunctional causes should be borne in mind. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated. 7. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 8. Any possible influence of prolonged NORINYL-1 therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. 9. A decrease in glucose tolerance has been observed in a small percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving NORINYL-1 therapy. 10. Because of the occasional occurrence of thrombophlebitis and pulmonary embolism in patients taking oral contraceptives, the physician should be alert to the earliest manifestations of the disease. 11. Because of the effects of estrogens on epiphyseal closure, NORINYL-1 should be used judiciously in young patients in whom bone growth is not complete. 12. The age of the patient constitutes no absolute limiting factor, although treatment with NORINYL-1 may mask the onset of the climacteric. 13. The pathologist should be advised of NORINYL-1 therapy when relevant specimens are submitted.

Side effects observed in patients receiving oral contraceptives: The following adverse reactions have been observed in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea, edema, chloasma or melasma, breast changes (tenderness, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretion, suppression of lactation when given immediately postpartum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals, mental depression.

Although the following side effects have been reported in users of oral contraceptives, no cause and effect relationship has been established: anovulation post-treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, itching.

The following occurrences have been observed in users of oral contraceptives (a cause and effect relationship has been neither established nor disproved): thrombophlebitis, pulmonary embolism, neuro-ocular lesions.

The following laboratory results may be altered by the use of oral contraceptives: increased sulfobromophthalein and other hepatic function tests, coagulation tests (increase in prothrombin, Factors VII, VIII, IX and X), thyroid function (increase in PBI and butanol extractable protein-bound iodine and decrease in T^3 values), metyrapone test, pregnanediol determination.

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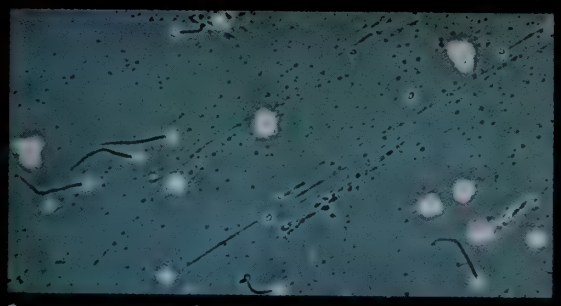
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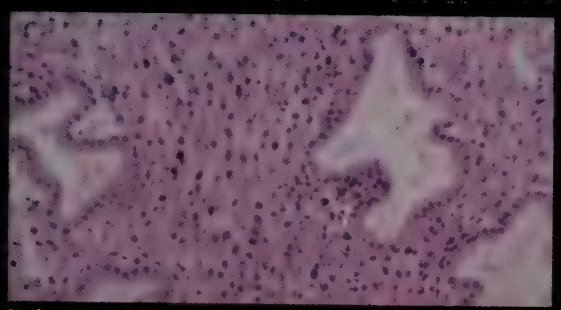
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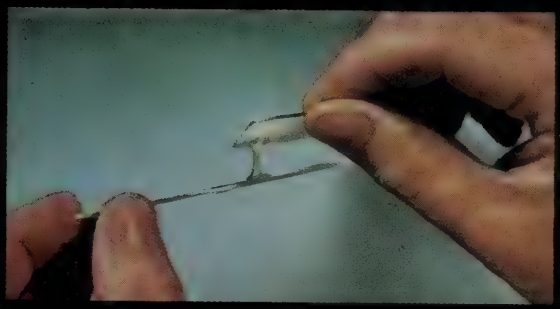


Spermatozoa appear healthy, active, freemoving.

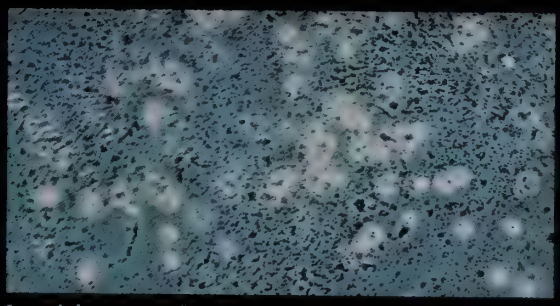


Endometrium of untreated patient is receptive to the fertilized ovum during secretory phase.

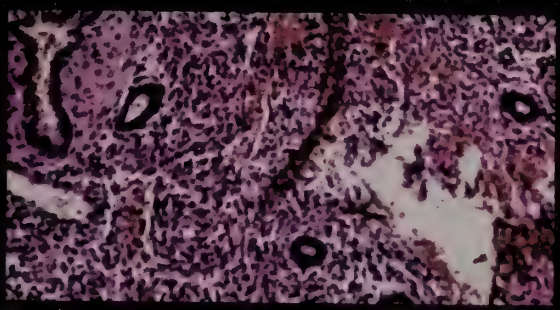
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Immobile spermatozoa as they appear in cervical mucus taken from patient treated with Norinyl-1.



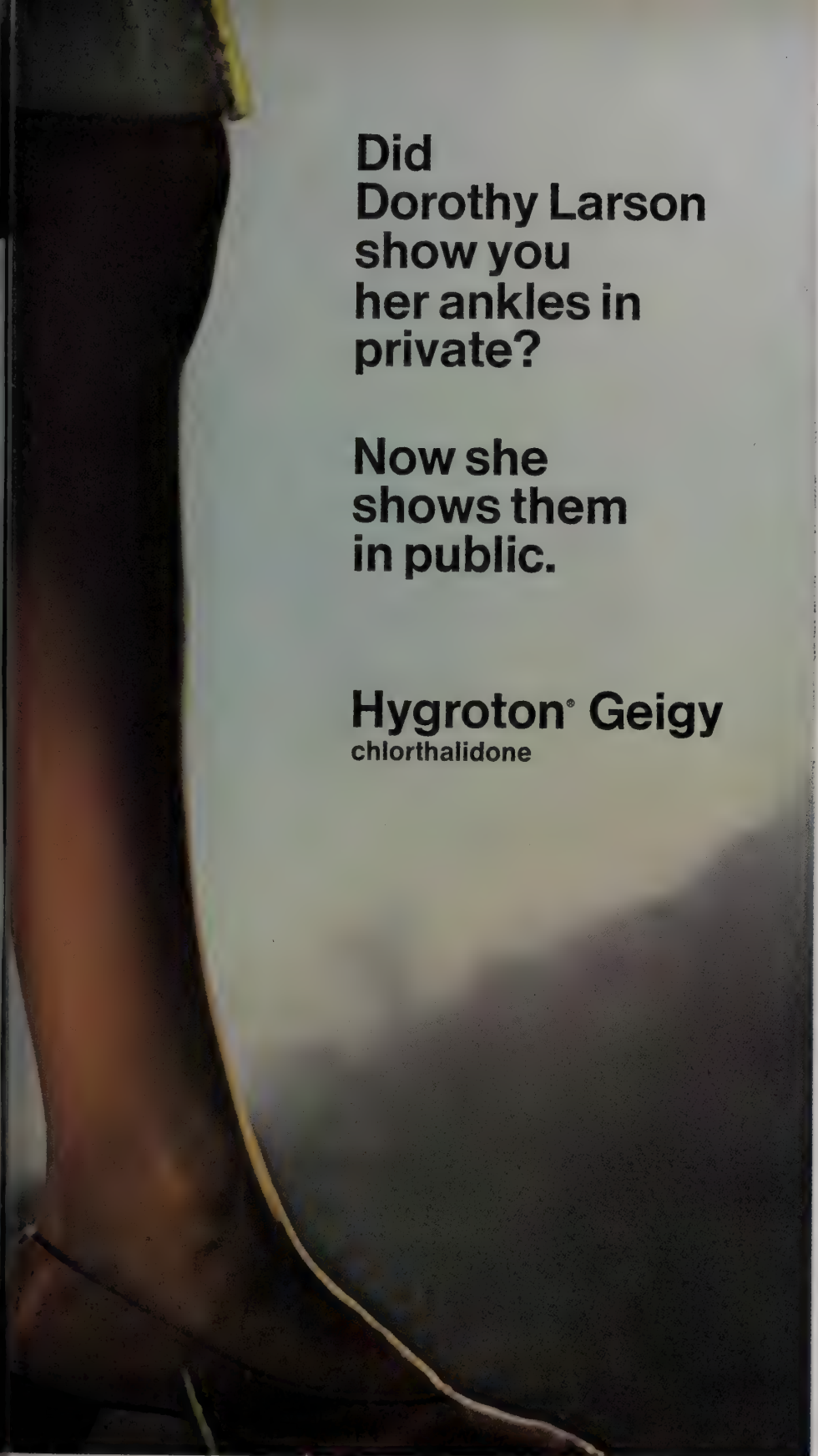
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Warning: With the administration of enteric-coated potassium supplements, which should be used only when adequate dietary supplementation is not practical, the possibility of small bowel lesions (obstruction, hemorrhage, and perforation) should be kept in mind. Surgery for these lesions has frequently been required and deaths have occurred. Discontinue enteric-coated potassium supplements immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur. Use with caution in pregnant patients, since the drug may cross the placental barrier and adverse reactions which may occur in the adult (thrombocytopenia, hyperbilirubinemia, altered carbohydrate metabolism, etc.) are potential problems in the newborn.
Precautions: Antihypertensive therapy with Hygroton should always be initiated cautiously in postsympathectomy patients and in patients receiving ganglionic blocking agents or other potent antihypertensive drugs, or curare. Reduce dosage of concomitant antihypertensive agents by at least one-half. Barbiturates, narcotics or alcohol may potentiate hypotension. Be- cause of the possibility of progr sion of renal damage, periodic determination of the BUN is indi cated. Discontinue if the BUN ris or liver dysfunction is aggravate Hepatic coma may be precipitat Electrolyte imbalance, sodium a or potassium depletion may occ If potassium depletion should oc cur during therapy, Hygroton sh be discontinued and potassium supplements given, provided the



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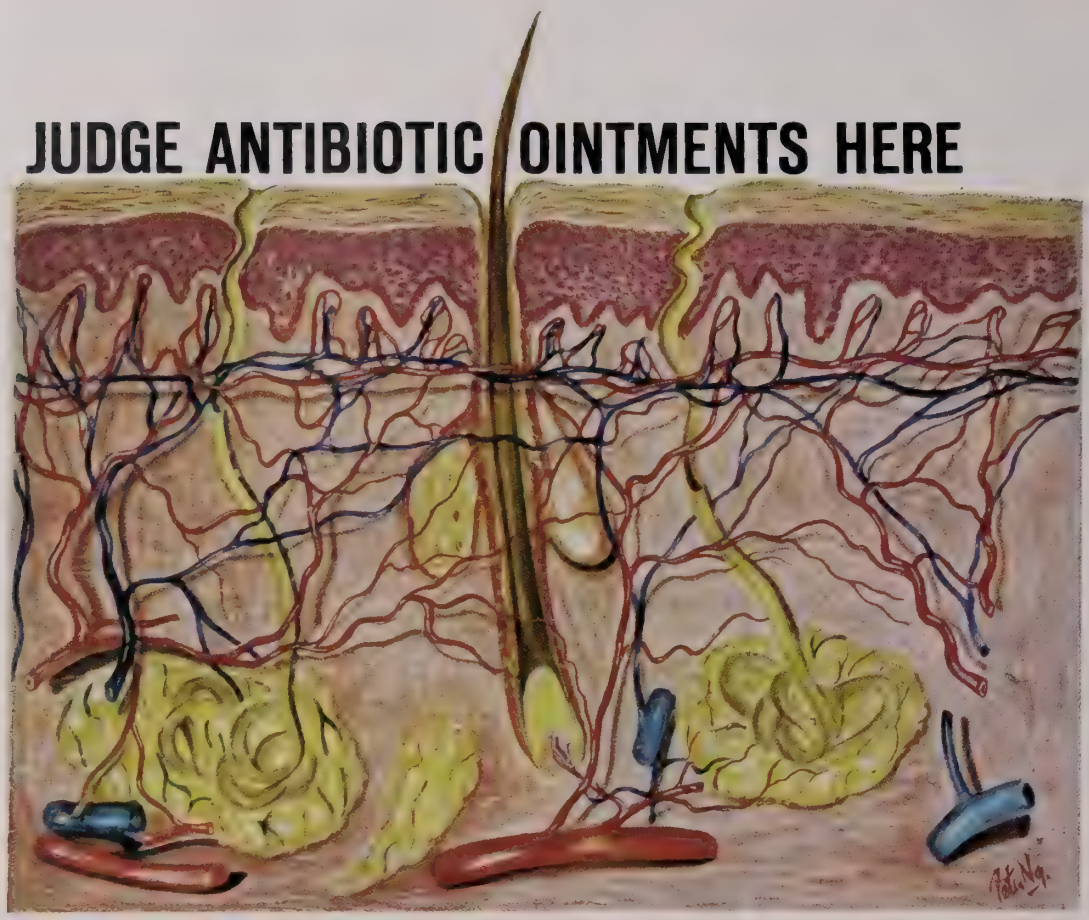
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Clinical Path Conference

A Fetal Complication with Maternal Diabetes

Case History

Dr. Robert L. Strom:*

A 2930-gram male infant was born to a 22-year-old Caucasian primagravida whose pregnancy was complicated by preeclampsia, polyhydramnios and diabetes mellitus. The first stage of labor lasted six hours and forty-five minutes; the second stage, thirty minutes; and the third stage, five minutes. Medication during labor consisted of Largon 20 mg. i.m.; the anesthesia was 1% xylocaine by local infiltration. The placenta appeared normal and three vessels were present in the edematous umbilical cord. Upon delivery, no heart beat or spontaneous respirations were noted. The child was suctioned, intubated, and given 0.1 cc. of 1:1000 epinephrine and 10 cc. of sodium bicarbonate by intracardiac injection. A good heart beat was obtained after eight minutes, and spontaneous gasps began at ninety minutes. After three hours, respirations were normal but muscle tone remained flaccid.

The cord blood type was A negative. The cord hemoglobin was 14.4 grams % with 12,100 white blood cells per cu. mm. and 75 nucleated red blood cells. The initial cord blood sugar was 310 mg.%. Two hours later the infant's blood sugar was 57 mg.%. An intravenous infusion of 10% dextrose in water was initiated. Cord blood electrolytes were: sodium 122, mEq/L, potassium 5.8 mEq/L, chloride 87 mEq/L, CO_2 18 mEq/L, and calcium 10 mg.%. A urine specimen showed a pH of 5.5, and an albumin of 2+ with no sugar or acetone. Microscopic examination of the urinary sediment revealed occasional granular casts and one to two white blood cells per high-powered field.

The rectal temperature was 98°F., the pulse was 144 per minute, and the respirations were 32 per minute. The skin revealed multiple ecchymoses with facial petechiae. The anterior fontanel was 1 × 1 cm. and the head was moderately molded. The color was mottled with cyanosis of the distal parts. Auscultation of the lungs revealed a few rales over the right upper lobe with no retractions and good air exchange. The heart tones were normal. In the right abdomen a firm smooth mass was palpated extending from the costal margin downward to the pelvic rim, not crossing the midline. The liver was palpable 1 cm. below the right costal margin. Neurological examination revealed generally poor muscle tone and no Moro reflex. A chest x-ray, a flat film of the abdomen, and an intravenous pyelogram were performed. The child suffered a cardiorespiratory arrest 13 hours after birth and expired.

Clinical Discussion

Dr. Roger Herdman:*

This male infant was born to a young white primagravida who had several complications of pregnancy including preeclampsia, diabetes, and polyhydramnios, all of which I think have some bearing on the ultimate clinical course of her child. There is no mention in the protocol of whether the

*Associate Pathologist, Hennepin County General Hospital.
**Assistant Professor of Pediatrics, University of Minnesota.

baby was full term. However, since the birth weight was somewhat low for a diabetic mother, I shall assume that the baby was somewhat premature and may have had some intrauterine dwarfing. The presence of three cord vessels was presumably reported since it is well known that if there is only one umbilical artery, the incidence of anomalies in the child is much higher. The delivery itself sounds normal; however, the child was essentially dead and, after being resuscitated, was never neurologically normal.

As the mother's blood type is not stated in the protocol the possibility of ABO incompatibility cannot be commented upon. The cord hemoglobin was a little low and nucleated red blood cells were seen, as is commonly the case in babies of diabetic mothers. The cord electrolytes were somewhat abnormal, and I would interpret this set of chemical values as indicating that the mother was having some difficulty with the control of her diabetes at the time of delivery. A few hours later the child's blood sugar was a normal 57 mg.%. On the basis of recent data, blood sugar determinations in newborns mirror very poorly the actual blood sugar levels, since the cord blood sugars when monitored continuously may vary as much as 20 to 30 mg.% over a one- or two-minute period.

I would like to say a word here about the use of resuscitative electrolyte solutions in newborns. I do not think fluid management was a problem here, since this baby was given about 20 milliosmols over a four-hour period. The use of concentrated sugar solutions to resuscitate infants may lead to an increased total osmolar load. Hence it is recommended that no more than 25 milliosmols per kilo body water be given over a four-hour period.

The electrolyte situation seemed to improve and a very scanty urine specimen was obtained, which showed 2+ albumin and very little else. Newborns are allowed to put out about 250 mg. of protein per square meter; however, I think the 2+ albuminuria should be considered an abnormality and a valuable diagnostic clue to what was going on in this child.

The ecchymoses and petechiae seen on the baby could have been associated with the delivery, since petechiae on babies' faces are frequent with vaginal deliveries. However, in this child's particular circumstances, the petechiae may have been an expression of a bleeding tendency. An alternative explanation for the petechiae may have been thrombocytopenia due to sequestration of platelets into a large hemorrhagic area in the body cavity. The presence of acidosis is known to increase the bleeding tendency. Systemic defibrination may have occurred with circulating fibrin degradation products acting as antithrombins.

Then we have mention of the very large mass in the right side of the abdomen, with the lower edge of the liver apparently palpated above the mass. After a limited number of x-ray studies, the child expired. I think at this time it would be appropriate to view the x-ray films.

Radiologic Findings

Dr. Oscar Lipschultz:*

A number of these films were taken in an attempt to demonstrate the kidneys and the lower urinary tract. On the flat plate of the abdomen (Figure 1) air was seen in the small bowel, but the significance of this finding is open to question in a newborn infant. I get the impression that there is some increased density to the right of the midline in the area of

*Attending physician, Department of Radiology, Hennepin County General Hospital.

the mass. I cannot adequately define the limits of the mass but we do not see the renal outline. I doubt very much that the mass is the liver since it is circumscribed in a manner that I would not associate with hepatic masses. On the intravenous pyelogram study, the kidneys did not function, and I wonder whether perhaps the administered dosage was not large enough to visualize them. Then we have a film of the chest which shows the cardiac size to be at the upper limit of normal. The vascular markings in the lung fields do not suggest a shunt at the cardiac level. I do not get the impression that the lungs show the nodularity that you would associate with atelectasis of the newborn or hyaline membrane disease.

I am of the opinion that this youngster was premature since I do not see the epiphysis for the distal femur on either side.

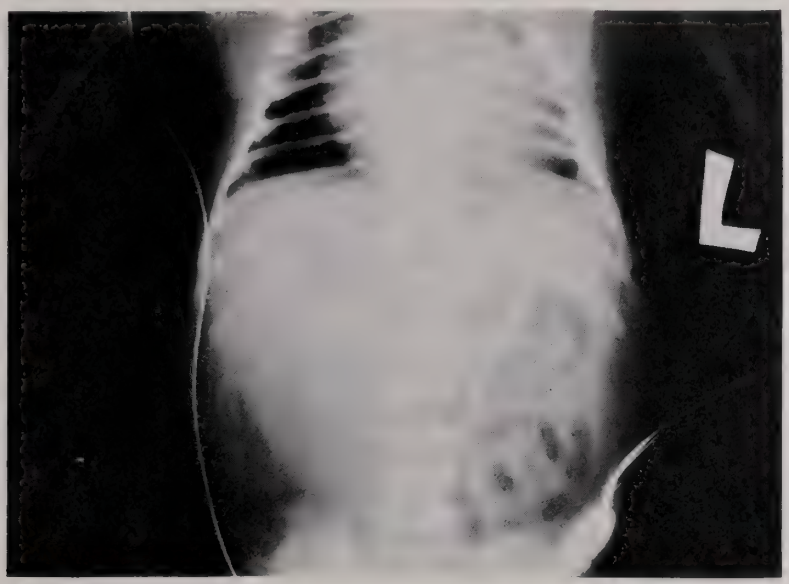


Fig. 1—Flat plate of the abdomen and chest x-ray: A mass density in the right abdomen displaces the small bowel gas pattern to the left abdomen.

Discussion

Dr. Herdman:

I am going to assume that the intravenous pyelogram was done correctly, that there was no visualization of the urinary tract, and that the chest film is within normal limits. I think there are two problems of interest here. First, what is the nature of the mass and why are the kidneys not functioning? And second, what caused the child's demise? I am going to attack the problem of the differential diagnosis of abdominal masses in newborns initially.

Abdominal Hematomas

Hematomas do occur in newborns, particularly involving the liver, spleen, or retroperitoneal space. However, I do not think that this consideration is germane since an abdominal hematoma does not explain the absence of kidney function. The mass was on the opposite side from the spleen and was well localized, with nothing to suggest that it was retroperitoneal.

Renal Abscess

Another consideration might be a renal or perinephric abscess. I would

exclude this also since there were no particular signs of infection, such as high fever or leucocytosis. The cord was described as edematous but did not appear infected, and there were no other portals of entry for infection.

Abdominal Tumors

Tumors represent a logical explanation for an abdominal mass in infancy. The prime possibilities are retroperitoneal lymphangiomas, teratomas, retroperitoneal hemangiomas, neonatal Wilms's tumors,* or neuroblastomas. With the exception of neuroblastoma, Wilms's tumor and possibly teratoma, these do not fully explain the absence of renal function bilaterally. The presence of an abdominal tumor does not really explain why this child was so ill. It is convenient to assume that the mass and the illness were related, although this is not necessarily true. Since the child was premature and was born of a diabetic mother with associated complications, his demise does not necessarily have to be related to the abdominal mass. At any rate, if the child did have a renal tumor, I believe the collecting system should visualize to some extent. If this was an adrenal hemorrhage, one might expect that the intravenous pyelogram would also visualize.

Polycystic or Multicystic Kidneys

I think that there are two other disease entities which commonly give rise to renal masses in children. The first is polycystic or multicystic kidney. A cystic kidney in the abdomen of an infant either does or does not function. If it functions, it is usually classified loosely as a polycystic kidney; if it does not function, it is generally termed a multicystic kidney. Multicystic kidneys are important mainly because they tend to be unilateral. If they are bilateral the child has no functioning renal tissue; if they are unilateral, the urinary drainage system is frequently anomalous. There is a possibility that this child had a multicystic kidney on the right and obstructive uropathy with nonfunction on the left. This would explain the bilateral nonvisualization on intravenous pyelogram and the morbidity of the child. However, if this were the case, one would expect to palpate the obstructed hydronephrotic kidney on the left. Another factor to be considered is the character of the right-sided abdominal mass. If it were a multicystic kidney, it should have been lumpy and uneven to palpation. Therefore, I am not too strongly attached to the diagnosis of cystic disease of the kidneys.

Obstructive Uropathy

Another common cause of renal masses in children is obstructive uropathy. Here again, in order to have nonvisualization of both kidneys, the obstruction would have to be bilateral; it would be quite unusual to have one kidney so massively enlarged and the other completely normal. It would also be difficult to explain the child's sudden demise. After all, he did not die of uremia. It would be impossible to die of uremia after being on dialysis in utero 12 hours before.

Renal Vein Thrombosis

Now I will proceed to discuss the entity I think the child had. I believe that this is a classic case of renal vein thrombosis. It is going to be difficult,

*See Test Your Word Score Page 649.

however, to predict whether the adrenals were involved and exactly what caused the rapid demise.

Why are infants of diabetic mothers so prone to thrombosis? This child was dehydrated at birth; in fact, most infants of diabetic mothers are dehydrated. They may be heavy, but that is due to excessive fat. Their total body water is low. This may be the reason that they are predisposed to thromboses in general, and to renal vein thrombosis in particular. Such infants have roughly 15 to 20 times the incidence of thromboses in general, and the renal vein heads the list as a site of thrombosis, with the adrenal vein not far behind. Many of these thromboses in infants of diabetic mothers occur in utero, are of some duration at birth, and show different thrombus morphology from that of other infants dying of thromboses. Infants of diabetic mothers with renal vein thrombosis tend to die very early as opposed to children of nondiabetic mothers. Another valuable clue here is the fact that this child was born of a mother with toxemia and polyhydramnios, which in children of diabetic mothers are common predisposing factors to renal vein thrombosis. In infants of nondiabetic mothers, sepsis, postoperative complications, and diarrhea are much more common causes of thromboses.

I want to take a few minutes to talk about renal vein thrombosis in general. Infants under two months of age represent a high-risk group for development of this complication, although there is a significant incidence of renal vein thrombosis after the first few weeks of life. It is interesting to speculate on why the clinical symptomology of renal vein thrombosis is so varied, extending from total anuria to complete recovery even in cases of bilateral thrombosis. Some children develop the nephrotic syndrome. I think that the anatomic sites of thrombosis and the speed with which they are occluded hold a valuable clue to the ultimate prognosis of this disease. This particular child, judging from the massive swelling of the kidney, the toxicity, and the sudden demise must have rapidly infarcted the total kidney. This is not necessarily the case in other instances, however, where, even if there is bilateral involvement, there may be spontaneous recovery. The degree of recovery relates to the amount of collateral venous circulation that remains patent.

Adrenal Vein Thrombosis

The adrenals are not infrequently involved and I think this may be a possibility. There is an interesting case in the literature where the adrenal was involved, and from the histology of the adrenal gland, which was fossilized at a certain stage of development, the time of the infarction could be accurately estimated. There is nothing in the protocol here that indicates whether adrenal involvement was present or not.

Operative Management of Renal Vein Thrombosis

The next question one might ask is: Should anything have been done for this child? I think not. Although most people recommend nephrectomy, which may result in a rapid recovery, there is body of opinion that suggests only medical observation. In view of this child's borderline clinical status, I believe he falls into the group of patients which should not be operated.

Intracranial Hemorrhage

Is there anything else which could explain this child's acute demise? I

mention this for completeness although there is no evidence in the protocol other than the depressed neurologic state. Very frequently these children have intracranial hemorrhage, although I think the renal complications alone would have been sufficient to cause this child's demise.

Clinical Diagnoses: 1. Renal vein thrombosis
2. Intracranial hemorrhage

Pathology

Dr. Strom:

On postmortem examination the baby had a few petechiae and ecchymoses over the head, face and scalp suggesting minimal birth trauma. The heart appeared to be slightly enlarged since it weighed 25 grams, and we would have estimated that the heart in a baby this size should weigh about 18 grams. There was a small patent ductus which probably caused no physiologic embarrassment.

Neonatal Atelectasis and Hyaline Membrane Disease

The lungs weighed 30 grams each and did not float when we placed them in water. There appeared to be some neonatal atelectasis of the lungs. A small amount of scattered hyaline membrane disease was present although the degree did not suggest that respiratory distress syndrome was a major component of this child's illness. Some polymorphonuclear leucocytes and round cells were present in the alveolar spaces suggesting early bronchopneumonia.

The liver weighed 125 grams and was somewhat enlarged. Between the liver cords we observed a significant amount of extramedullary hematopoiesis. This is seen in erythroblastosis fetalis, but also in prematurity alone without isosensitization. The spleen also showed some extramedullary hematopoiesis with proliferation of nucleated red blood cells.

Islet Cell Hyperplasia

The pancreas revealed increased numbers of islets of Langerhans, a closer view of which suggests that there was some islet cell hyperplasia (Figure 2). Islet cell hyperplasia does occur in infants of diabetic mothers in that the fetus attempts to supply the maternal needs for insulin. Hypoglycemia is not uncommonly seen in these infants after birth; however, this did not present a clinical problem in this case.

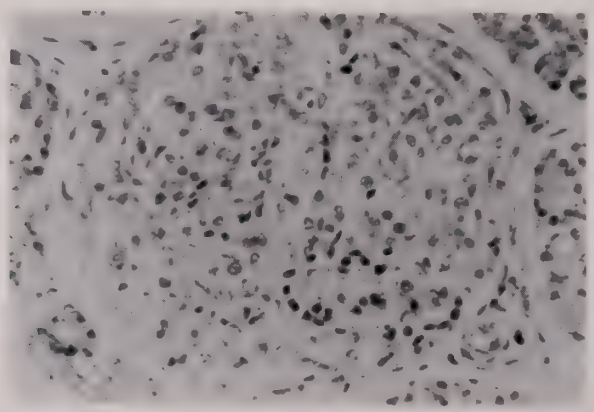


Fig. 2—Islet cell hyperplasia 45×.

Renal Vein Thrombosis

The abdominal mass was indeed a right kidney involved by hemorrhagic infarction; an in-situ photograph appears in Figure 3. The right kidney was significantly enlarged and there appeared to be some infarction of the right adrenal gland as well. The left kidney appeared uninvolved and very likely

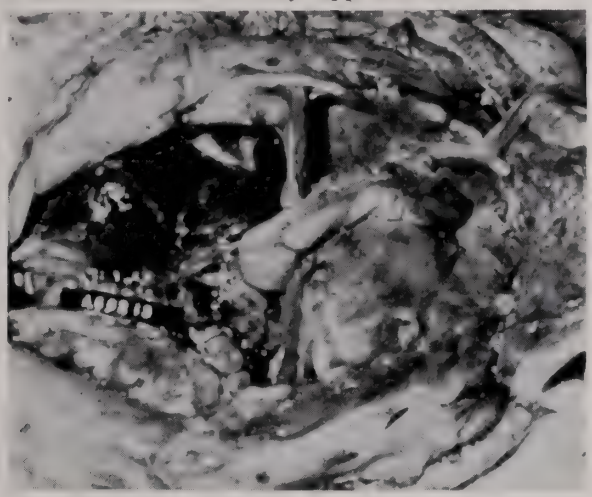


Fig. 3—Abdominal cavity opened to reveal the hemorrhagic infarction of the right kidney and adrenal at the top of the field.

put out a small amount of urine. I have no explanation for why it did not visualize on the intravenous pyelogram. The left adrenal did not appear to be significantly involved. The microscopic appearance of the kidney was that of hemorrhagic infarction; the thrombosed renal vein at the hilus is seen in Figure 4. Thrombosis was present in all radicles of the renal vein with early organization at the periphery. There was no evidence of recanalization. However, about the margin of some of the clots definite calcification could be seen. The calcium would suggest that the renal vein thrombosis was of some duration and probably occurred in utero. The left kidney was histologically normal and probably in good functional order.

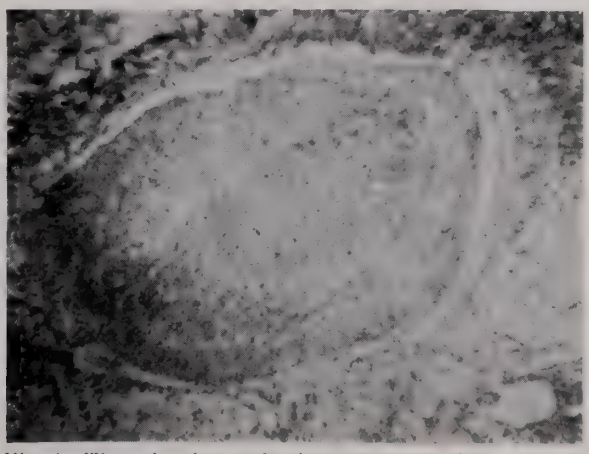


Fig. 4—Thrombus in renal vein at the hilus 45×.

The right adrenal gland was approximately 50% involved with hemorrhagic infarction. There was only a tiny focus of infarction in the left adrenal. The adrenal glands are sometimes involved with thrombosis of the adrenal veins, leading to a syndrome characterized by a very rapid respiratory rate and sudden death.

A few additional comments about renal vein thrombosis. In the large series reported by Abeshouse[1] there were 228 cases, 98 of which occurred in the first year of life. A total of 121 cases were unilateral: 57 on the left and 37 on the right.

Apparently the left kidney has a higher incidence of renal vein thrombosis, the highest incidence occurring early in life with approximately 50 to 60% of the cases appearing or being recognized in the first two months of life. There are several theories about why renal vein thrombosis occurs in these infants. One theory incriminates hydration, low fetal blood pressure, or birth trauma. Septicemia is incriminated in the older age group as well. In addition, in older infants there is an association between renal vein thrombosis and massive diarrhea, vomiting and dehydration. This is a well recognized entity and may be associated with fever and leucocytosis. Sometimes it is difficult to determine whether the diarrhea is initiated by the occurrence of renal vein thrombosis or whether the renal vein thrombosis is caused by the dehydration secondary to the diarrhea.

When Avery[2] called attention to the association between renal vein thrombosis and maternal diabetes in 1957 there were only four cases in the literature. Many more cases have since been recognized and treated surgically. There was thrombocytopenia in one of Avery's cases, and I note that we do not have a platelet count in this child. We do know that platelets are consumed with massive tissue infarctions, and the thrombocytopenia may be a clue to the presence of infarcted renal tissue. Minimal intracranial hemorrhage was present in the posterior fossa and over the cerebral convolutions.

Pathological diagnoses:
1. Right renal vein thrombosis with hemorrhagic infarction of the right kidney.
2. Focal infarction of right adrenal gland.
3. Neonatal atelectasis and mild hyaline membrane disease.
4. Intracranial hemorrhage.
5. Hyperplasia of the islets of Langerhans.

A Surgical Resident:

I was a little surprised when you said that nothing could be done for this child. Say the infant had lived for 24 hours, assuming you based your diagnosis mainly on history and the maternal diabetes, would you say that he should have been taken up to surgery for removal of the abdominal mass?

Dr. Herdman:

Certainly. There are similar case reports in the literature of children who did very well following surgical removal of the involved kidney. If you can bring yourself to operate on a child in such poor condition, there is a good chance that removal of the mass will decrease the toxicity.

Robert L. Strom, M.D.*
Hennepin County General Hospital

*Associate Pathologist.

References

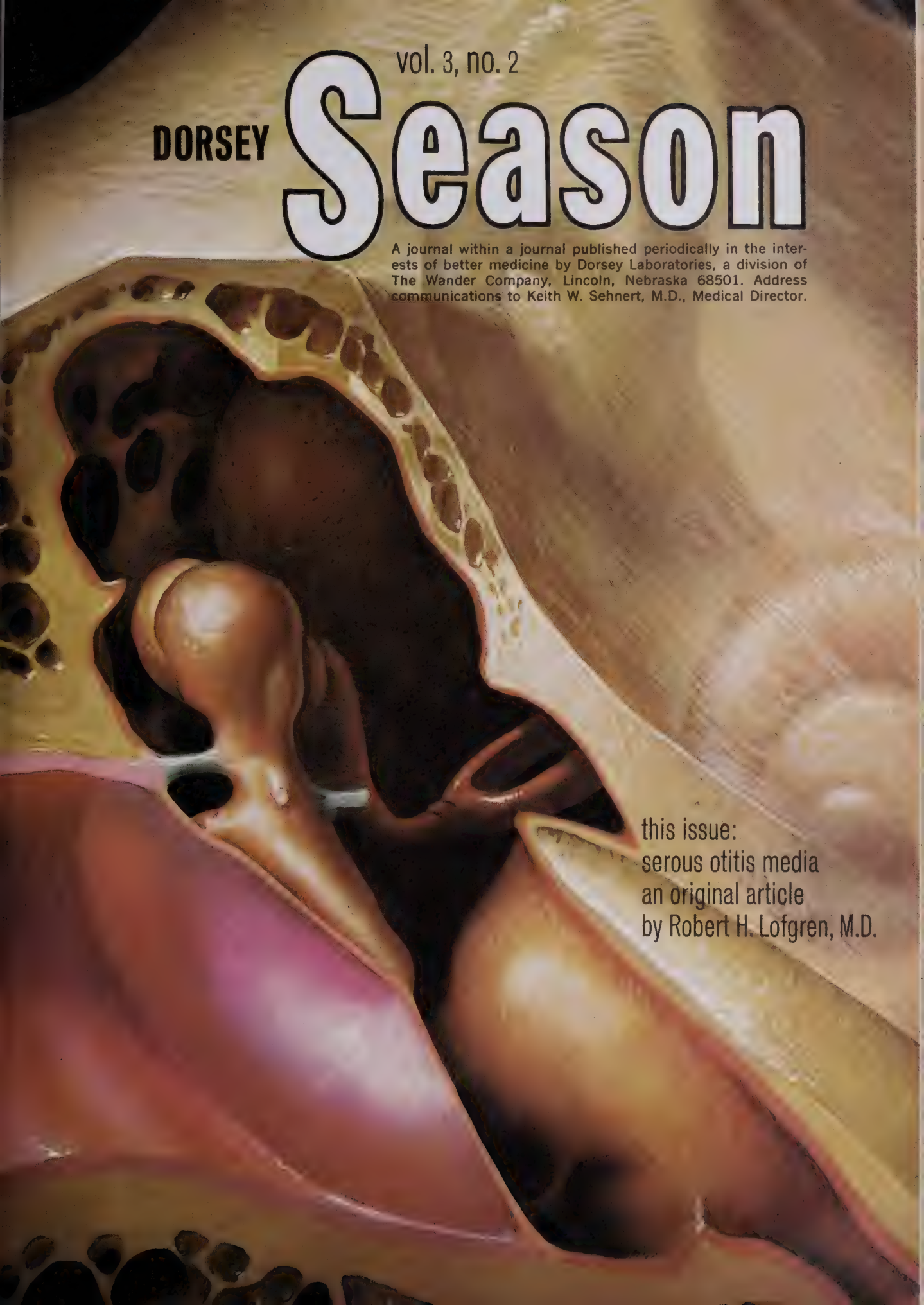
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Only the wise possess ideas; the greater part of mankind are possessed by them.—Samuel Taylor Coleridge

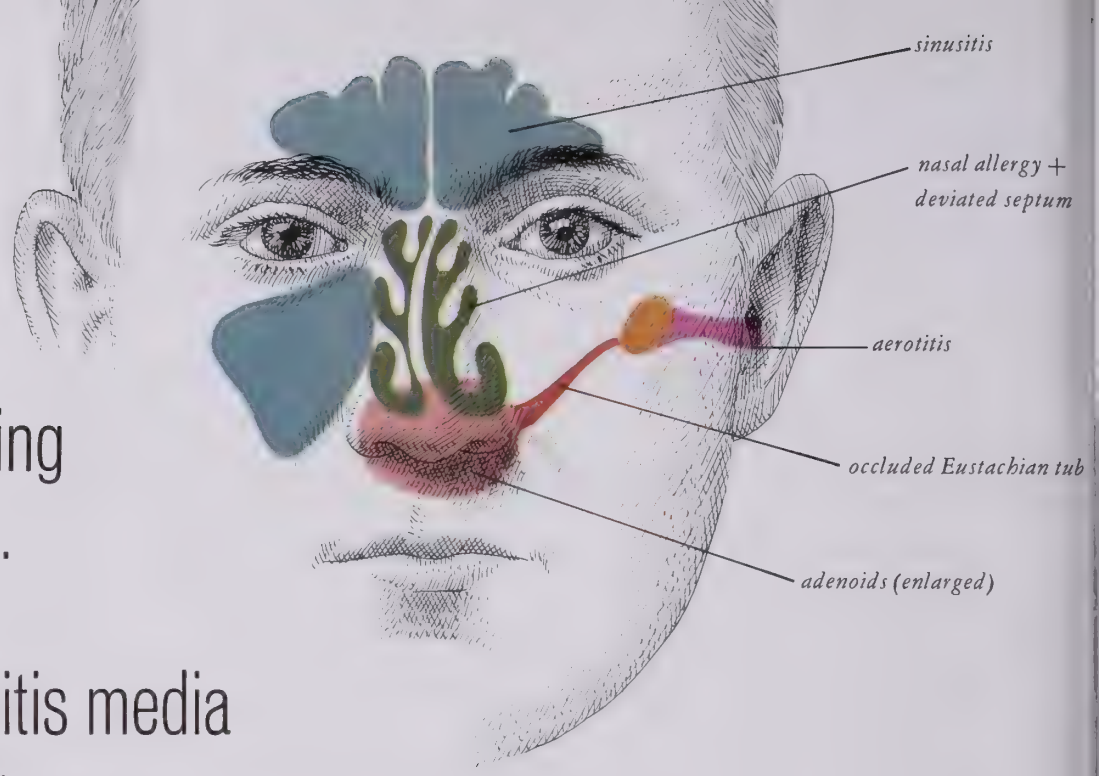
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this issue:
serous otitis media
an original article
by Robert H. Lofgren, M.D.



the complaining earache... key to serous otitis media

Robert H. Lofgren, M.D.
Associate Surgeon, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts

Serous otitis media is probably the most common ear problem in children, especially in the wintertime. Diagnosis is usually easy in adults, but may be quite difficult in children, especially the very young child where one has to depend almost entirely on the physical findings.

The symptoms of serous otitis are a fullness in the ear, a mild hearing loss and mild earache. The earache can best be described as a "complaining earache" instead of a "screaming earache" as found in purulent otitis media. A young child may be irritable and pull at the ear. In milder cases, and as the ear recovers, gurgling and popping noises can be heard in the ear.

On examination one may see a yellow tympanic membrane and if a fluid level is present the diagnosis becomes easy. However, the eardrum may be dull gray, or slightly pink, or even perfectly normal. Pneumomassage using a Siegle otoscope or a closed-head electric otoscope must be done on both ears, otherwise the diagnosis will be frequently missed. Attempted movement of the drum with the pneumatic otoscope produces either a sluggish motion of the drum or no motion at all instead of the easily movable normal drum. The Rinne test is negative and there is a 15-20 decibel conductive hearing loss. The bone conduction may be better than normal and an air-bone gap may exist even with the air conduction within normal limits. Occasionally one finds a false nerve deafness on the audiogram when thick glue-like fluid causes immobility of both the oval and round window. Both conditions return to normal when the fluid is removed, but they make the interpretation of screening audiograms very difficult.

There is no single cause for serous otitis. One factor always present is blockage of the eustachian tube, but this alone is not enough to produce fluid. There must also be an inflammatory reaction. Blockage of the eustachian tube may be caused by many conditions. In children the most common cause is enlarged adenoids. In the summer the next most common cause is allergy. Upper respiratory infections or influenza are common causes in the winter. Nasal allergy, acute and chronic sinusitis, nasal septal deformity and cleft palate can all cause eustachian tube obstruction. Some children may have a congenitally small eustachian tube, but fortunately they usually "grow out of the problem."

The first sign of a nasopharyngeal tumor is often a serous otitis. One must always rule this out in any adult who later in life develops repeated or persisting serous otitis. Causes sometimes overlooked are nasogastric tubes after surgery, simple obesity and cardiorenal disease, which may produce congestion in the mucosal lining of the eustachian tube. In recent years we have been seeing a new cause—acute otitis media, where the patient is adequately treated with antibiotics but where drainage has not been

established either through the eardrum or down the eustachian tube. A sterile exudate is left in the middle ear.

The inflammatory response may be caused by a marked negative pressure as in air otitis from flying, or it may be from a mild bacterial or viral infection in the middle ear. Serous fluid is a good culture medium and will frequently go on to purulent otitis media, especially if the original blockage was caused by an infectious process such as acute rhinitis or adenoiditis. When the infection heals there may be scarring in the middle ear mucosa. Mucous glands develop in this tissue and pour out a thick mucoid material. This ear usually looks normal until a pneumatic otoscope is used. The objectives in treating serous otitis are to remove the obstructing agent and to provide drainage from the middle ear. Often this can be accomplished by decongestants and nose drops. If large obstructing adenoids are present they should be removed. Sinusitis should be treated with oral decongestants or nose drops, plus antibiotics where indicated. Nasopharyngeal tumors should be treated. Allergies should be treated with antihistamines and, where indicated, by desensitization.

If the fluid does not clear with medical treatment within a week or two, a myringotomy should be done. If there is a question of active infection or if the fluid looks purulent, as is seen at the conclusion of acute otitis, cultures are taken. On adults this can be done in the office without anesthesia. It is no more painful than an intravenous needle for a blood test. A good safe topical anesthetic has a tremendous psychological value to the patient. Children under the age of 1 require no anesthesia. Between the ages of 1 and 3 anesthesia is not absolutely essential although a general anesthetic may be used to avoid the child's possible mistrust at follow-up examinations. I usually do the myringotomy at the same time as the adenoidectomy if the adenoids are enlarged. Once drainage has been established with decongestants or by myringotomy, positive pressure inflation of the middle ear is invaluable in forcing out the serous fluid and keeping it from reforming. The patient can do this himself by performing the Valsalva maneuver. This should be done several times a day, by taking a deep breath, holding the nose and blowing hard against the closed lips for a second or two.

In resistant cases where the fluid reforms as soon as the myringotomy heals, small polyethylene tubes are inserted through the myringotomy site. Insertion of the tubes, even in adults, usually requires an anesthetic. Good anesthesia can be obtained by infiltrating the canal wall with a local anesthetic, using a #27 needle. Once inserted the patient has no sensation of the tubes' presence. Be careful to caution the patient or parents not to allow any water to get into the ear canal while a myringotomy is open or a tube is in place. Water can be kept out by a pledget of lamb's wool in the ear canal or a cotton pledget thickly coated on the outside with petroleum jelly. I check these patients a week after a myringotomy to be sure it is healed and at two month intervals until the tubes have fallen out, usually within three to six months after insertion.

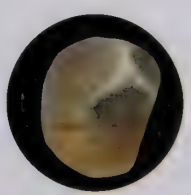
The mucoid type of fluid is so thick and tenacious that it is appropriately called a glue ear. It is aspirated only with difficulty through the eardrum, and occasionally must be removed through a tympanotomy. This thick, glue-like fluid is prone to recur, as the myringotomy usually heals long before the mucous membrane has returned to normal. Repeated myringotomies, as many as ten or twenty, were formerly required for this condition. Now polyethylene tubes are inserted initially when this thick, glue-like material is found. At times a subacute mastoiditis may accompany the serous otitis, which will necessitate a simple mastoidectomy before the condition can be eradicated. Usually the thin serous fluid readily responds to decongestants or to a myringotomy and removal of the eustachian tube obstruction. Occasionally, however, even serous fluid will repeatedly reform. For this, resection of the tympanic plexus of nerves which lies on the promontory of the middle ear has been carried out, as the tympanic branch of the glossopharyngeal nerve is the secretomotor nerve to the ear.

Failure to diagnose serous otitis is the most common cause of the recurrent, almost continuous otitis me-

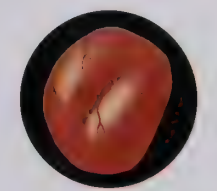
Otoscopic Views



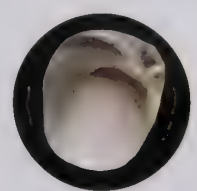
Normal



Acute Serous



Acute Purulent



Chronic Serous

dia seen in young children. In these cases a myringotomy will frequently provide a long-term cure without adenoidectomy or any other surgery. Failure to do this may allow the condition to go on to acute or subacute mastoiditis. Adhesive otitis media with scar tissue binding down the ossicles or tympanosclerosis may also result with permanent impairment of hearing. The prognosis for hearing with adhesive otitis or tympanosclerosis is usually poor. If the adhesions are removed, they reform, and the same is frequently true of tympanosclerosis even after a tympanoplasty. For many of these people a hearing aid is the only solution. The constant negative pressure in long standing serous otitis media may draw in either Schrapnell's membrane or the posterior superior portion of the eardrum forming a pocket to cause a chronic otitis media with cholesteatoma, which may not become apparent until twenty or thirty years later.

The non-medical complications of improper diagnosis or treatment may be even more serious. The irritable child, the frequent bouts of acute purulent otitis media with pain and fever, the expense of antibiotics and doctors, and the time lost from school or work affect the entire family.

In summary, serous otitis has many causes. There is a blocking of the eustachian tube and an inflammatory reaction in the middle ear mucosa, the latter usually caused by a mild infection. The treatment is to provide immediate drainage by decongestants and where necessary, by a myringotomy. The obstructing agent must be removed by surgery if it is adenoid or by oral decongestants, and antihistamines or nasal spray if it is an upper respiratory infection or allergy. Occasionally resistant cases require plastic tubes placed through the eardrum or other more radical surgery. Failure to treat properly leads to hearing loss which may be permanent, repeated acute otitis media or possibly even chronic otitis media with cholesteatoma.

References 1. Senturia, B. H. et al.; Middle Ear Effusions: Pathologic Changes of the Mucoperiosteum in the Experimental Animal, Ann. Otol. 71:632-648, 1962. 2. Grahne, B.; Serous Otitis Media, Acta Oto-Laryng. 58:1-8, 1964. 3. Sade, J.; Pathology and Pathogenesis of Serous Otitis Media, Arch. Otolaryng, 84:297-305, 1966. 4. Buckingham, R. A. and Ferrer, J. L.; Reversibility of Chronic Adhesive Otitis Media with Polyethylene Tubes, Laryngoscope 76:993-1014, 1966. 5. Chalat, N. I. and Lounsbury, E.; A Hearing Phenomenon and Serous Otitis, Laryngoscope 76:983-992, 1966. 6. Shucknecht, H. F.; Chronic Otitis Media in Children: A New Treatment, Clin. Pediat. 3:718-727, 1964. 7. Feuerstein, S. S.; Surgery in Serous Otitis Media, Laryngoscope 76:686-708, 1966. 8. Kapur, Y. P.; Serous Otitis Media in Children, Arch. Otolaryng. 79:38-48, 1964. 9. Silverstein, H., Miller, G. F., Jr. and Lindemman, R. C.; Eustachian Tube Dysfunction as a Cause for Chronic Secretory Otitis in Children, Laryngoscope 76:259-273, 1966.



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Abstracts, Briefs and Commentaries

ULTRASONIC PULSE DETECTION

The simplest way of determining blood flow is palpation, but only very limited parts of the arterial system are palpable. Other methods can be used, such as arteriography, plethysmography, xenon-clearance and skin temperature measurement. A new method for evaluating the arterial blood supply in the extremities is described in detail, based on the use of reflected ultra sound, which has frequencies higher than the human ear can hear.

Reflected ultra sound has been used to register the movement of the anterior cusp of the mitral valve. Donald & Brown have mentioned its use for the diagnosis of aneurysms of the aorta, and Howry has employed it to demonstrate the large vessels of the extremities and neck. It has also been used to estimate the flow in blood vessels.

The principles of this new method are explained in considerable detail. There is no difficulty registering the pulse in a single artery along the extremity, but it is difficult to distinguish between branches of arteries that are close together. This new way of examining the arterial system is considered an improvement when the pulse is too weak to be palpated or when the vessel is too deep to palpate. The method is intended for the following purposes: diagnosis and localization of emboli, traumatic lesions of the arteries, evaluation of the pulsations in big arteries in chronic obliteration, continuous registration of the pulse distal in the extremity when operating on its arteries, and postoperative evaluation of the pulsation in the extremity after operation on its arteries.

Stanley R. Maxeiner, Sr., M.D.
Minneapolis, Minnesota

Holm, H. H. and Kristensen, J. Kvist: Ultrasonic Pulse Detection. From the Department of Surgery H, Gentofte Hospital, Hellerup, Copenhagen, Denmark.

THE DRUG PROBLEM AMONG YOUNG PEOPLE

"Turn on," "tune in," and "drop out." This statement has become the credo of a new generation of young people who have begun to solve their problems by the use of hallucinatory drugs. The taking of drugs is not a new

thing. For thousands of years various drugs have been used to alter human consciousness and distort reality. What is new, however, is the high incidence of participation among young people and the extent or encouragement of it by influential members of the literary and academic worlds.

Of all the hallucinogenic agents, LSD (lysergic acid diethylamide) and marijuana (cannabis) are most widely used. The chief objection to the use of LSD arises from a growing body of evidence that it produces irreversible changes in the life style and personality of those who use it. Physiological changes include impairment of the subject's ability to make realistic judgements and to retain rational beliefs. A person on LSD may feel he is omnipotent and hence impervious to certain laws of his environment. He may feel that he can jump out of a window without being hurt. There may be a preoccupation with isolated aspects of sensory experiences and with forms of thinking similar to psychosis. Most characteristic of all is the abandonment of long-term patterns of striving.

In the past, most drug users came from deprived socioeconomic backgrounds and preferred narcotics to other drugs. In general, the new users come from the middle class, have good educational background, and are often engaged in intellectual or creative pursuits. The physiologic effects of LSD have not been fully delineated, and the specter of genetic damage to this intellectual elite hovers over us.

The evidence of harmful effects of marijuana is less clear than for LSD. However, a study of individual case histories suggests that the use of marijuana does indeed entail risk. In most instances, marijuana does not cause the original psychologic conflicts; on the other hand, it contributes nothing to their solution, and in many instances may delay or prevent effective approaches to the solution of conflicts.

In one sense, it is misleading to talk about "the drug problem" as if it were an isolated phenomenon, for it is only one aspect of young people's position in contemporary society. If drug taking were not related to current social conditions and the individual's reactions to them, it would be much easier to deal with.

Among the young, experience with drugs has become a kind of social currency, a source of status and esteem. Within the drug movement, there is also an element of rebellion and protest against contemporary American society and its institutions. Young people are keenly aware of social injustice, the threat of nuclear war, and the ineffectiveness and downright hypocrisy of some persons in public authority. Some young people who take drugs reject all authority; on occasion their criticisms of society become so generalized that they reject most conventional values. Using drugs as a personal medium, they focus on their own subjective values and experience.

The methods by which alienated young people choose to show their disdain for conventional values make rational thinking about their behavior difficult for older people. Whereas the young usually put high priority on love, peace, idealism, and similar attributes, the appearance and behavior of some youth who take drugs often seem to be peculiarly designed to attract criticism. Long hair, outlandish fashions, lack of cleanliness, sexual laxity, disrespect for personal and public property, and a manner which appears arrogant and impulse-ridden frequently accompany experimentation with drugs.

We in the medical profession must find an effective way to deal with the drug problem, and it must involve respect for the individual taking drugs and

tolerance for their behavior. Drugs should be viewed as an incidental factor, considered in the same class as other forms of "acting-out" behavior and not as a central problem. We physicians are in a particularly good position to help educators in developing methods to cope with the problem. We must give the young people the facts in terms that can be clearly understood, without moralizing, and combine this approach with efficient enforcement of new legislation covering distribution of these drugs.

Robert L. Strom, M.D.
Minneapolis, Minnesota

Farnsworth, Dana L.: "The Drug Problem Among Young People." West Virginia Med J 63:433, 1967.

A STUDY OF 605 FATAL PULMONARY EMBOLISMS AND TWO SUCCESSFUL EMBOLECTOMIES

In this remarkable study from Heidelberg, Germany, all the fatal pulmonary emboli occurring at the University of Heidelberg Hospital from 1915 to 1960 (50 years) were reviewed. The incidence of pulmonary embolization clearly diminished following the two great wars. The authors feel this is due to a state of malnutrition in the general public. Body weight carried only scant prognostic significance. However, beyond the fourth decade of life, the incidence of embolism rose continually.

The time interval between the onset of acute, massive pulmonary embolism and death was less than 10 minutes in 76.2 percent. Only 17.2 percent survived more than 30 minutes. In 97 percent of the patients examined, the embolus originated from the lower half of the body. In only 11.4 percent was a small previous infarction noted. Two of six Trendelenburg operations for the extraction of pulmonary emboli were sucessful.

Theodore A. Peterson, M.D.
Minneapolis, Minnesota

Linder, F., Schmitz, W., Encke, A., Trede, M., and Storch, H. H., Heidelberg, Germany: A Study of 605 Fatal Pulmonary Embolisms and Two Successful Embolectomies. Surg Gynec Obstet 125:1:82, 1967.

A SCAVENGER'S SCRAPS

Every now and then as I scavenge through recent medical journals, I run across scraps of imaginative prose that seem worth saving and showing to others. Because these pieces are well written, they need no abstracts or commentary; they speak for themselves.

Once there was a disease called lupus because it was like a wolf in eating the flesh. Then there was another disease called lupus erythematosus, because it was like lupus, though it is not lupus. Then there was another, called lupus erythematosus disseminatus, because it was like L.E., though it is not the same disease. And now there is a disease called lupoid hepatitis, because it is (remotely) like L.E.D., though it is not the same disease. A singular chain of resemblances. Should not the last member properly be called lupoidoidoidoid? It is time someone capped pseudo-pseudohyperparathyroidism.*

Angered by intrusions and displeased with libations of amniotic fluid, fibrinolysin, silicone, antihistamines and corticosteroids, the gods of the peritoneum in vengeance create intestinal adhesions.**

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*In England Now. A Running Commentary by Peripatetic Correspondents, Lancet, page 1038, November 11, 1967.

**Intestinal Adhesions. (editorial), New Engl J Med 277:657, 1967.

And the Great Sun shone and the land waxed warm and the Academies proliferated. And they suffered mutations so that some societies were no longer royal nor even academic, nor even learned, and they covered the land. And their Proceedings increased and multiplied and underwent mitosis and mutations. And some societies developed without publications and some publications developed without learned societies, and some publications and societies lost their learning, and a great cloud of societies and publications lay over the land.†

Richard L. Reece, M.D.
Minneapolis, Minnesota

†And It Came to Pass. (editorial), JAMA, 202:431, 1967.

STUDIES IN CLINICAL SHOCK AND HYPOTENSION V. HEMODYNAMIC EFFECTS OF DEXTRAN

In this very significant study, 31 patients in shock, not due to blood loss, were treated with Dextran 75 or Dextran 40. Patients with elevated central venous pressure, indicating heart failure, were excluded from this series. After treatment, mean cardiac output increased, pulse decreased, blood pressure increased, urine output increased, and the patient's clinical picture improved. In 16 of the 31 patients, the hypotension was corrected by Dextran alone. The authors recommended consideration of Dextran for treatment of hypotension or shock, not due to blood loss.

Theodore A. Peterson, M.D.
Minneapolis, Minnesota

Cohn, Jay N., Luria, Myron H., Daddario, Robert C., Tristani, Felix E.: Studies In Clinical Shock And Hypotension V. Hemodynamic Effects Of Dextran. Circulation 35:2:316, 1967.

The Essence of Tragedy

"I have of late—but wherefore I know not—lost all my mirth, forgone all custom of exercise; and indeed it goes so heavily with my disposition that this goodly frame, the earth, seems to me a sterile promontory."

So spoke Hamlet from his spiritual abyss after the perfidious murder of his father by his uncle; his mother's violation of decency by her hasty marriage to the murderer of her husband; and the solemn adjuration of his father's ghost that his son avenge his monstrous murder. How can we assess the shattering impact on any sensitive soul of this concatenation of events?

How could Hamlet remain devoted to his mother when she had dishonored her husband's memory? How could he show filial respect and political allegiance to his uncle who had usurped the throne? How could he avenge his father's murder except by compounding the sin of murder—from which his soul recoiled? Through the alembic of his emotional conflict the enormity of his moral dilemma became intolerable. Is it any wonder then that he cut himself off from his familiar world by closing his conduits. Not that he failed to speak! Rather he failed to communicate!

Had Hamlet been less introspective and more extroverted at this critical juncture he might have been galvanized into action that would have resolved his spiritual crisis instead of being paralyzed by indecision. Powerless to act, incapable of relating to his world on the warm, human terms that constitute living, he identified himself with nothing more than the earthy components of his physical body. Hence he wonders aloud: "And yet, to me, what is this quintessence of dust?"

*See Editor's Soliloquy, page 651.



Book Reviews

Opening a book is like opening a door, Turning a leaf's like a bend in the lane.
—Nancy Turner

BURNS, SHOCK, AND PLASMA VOLUME REGULATION—Carl A. Moyer, Harvey R. Butcher. Publication Date: Oct. 1967. Price: $18.50. C. V. Mosby.

This book is an excellent text expressing the views of the two well known authors on two subjects, shock and burns, that need to be mastered by each practicing physician. Unfortunately the average physician is so battered by the reams of reading material on these subjects in the journals that he does not have the time or the patience to 'sift the wheat from the chaff.'

As one first peruses this text he is apt to become disinterested because of what seems to be an overuse of tables, graphs, and figures to document the experimental work and the case histories. This should not deter one from obtaining the book, however, because it is a classic.

The use of large quantities of Ringers solution with lactate in the treatment of shock, and the silver nitrate treatment of burns are two contributions worth writing a book about. The section on burns is particularly well written. Certainly the therapy of burns will continue to change as the years go by, but for the present we must pay heed to the therapy recommended by the authors, for their results speak for themselves. The salvage of an occasional patient with a third degree burn over 50% of his body is noteworthy—to do it in the majority of cases treated is a medical milestone.

H. H. Farley, M.D.
Minneapolis, Minnesota

PATIENTS, DOCTORS AND FAMILIES—Fay C. Lewis, M.D. Doubleday. Price: $4.95. Pages: 240.

From one University South Dakotan to another of the same vintage this reviewer extends his congratulations to the author who has expatiated on a large variety of human ills with a great deal of common ordinary horse sense.

Dr. Fay C. Lewis has called to our attention many functional ailments which every physician observes and understands, though he may be too impatient to deal with them properly. She has further revealed the numerous foibles and anxieties behind which some patients conceal their true illnesses.

This book should have its greatest value for "functional" patients suffering from psychosomatic disorders, and it should be recommended to them as profitable reading material by the physicians who must then rechannel their thinking.

If patients can be made to recognize and acknowledge these damaging processes Dr. Lewis will have more than adequately provided her bit for progress in the medical sciences.

Carl O. Rice, M.D.
Editor-in-Chief

SECOND DECENNIAL REVIEW CONFERENCE ON CELL TISSUE AND ORGAN CULTURE. National Cancer Institute Monograph 26. Pages: 229. Price $4.00. National Cancer Institute, Bethesda, Maryland, 1967.

The monograph is made up of papers presented before the Tissue Culture Association at Bedford, Pennsylvania, September 1966. Some of the topics were: Evidence for a "Governor" on protein synthesis in animal cells: Positive signals in serum, Genetic markers as tracers in cell culture, Histochemical approaches to cell characterization in vitro, Mechanisms of organogenetic tissue interaction, and "Spontaneous" neoplastic transformation of cells in vitro: Some facts and theories.

The paper on "Ultrastructural aspects of in-vitro development of monocytes into macrophages, epithelioid cells, and multinucleated giant cells" is provocative. The author describes the ultrastructure of the monocyte and its differentiation forms and illustrates them with 33 electron photomicrographs and five drawings. He concludes that the monocyte is the stem cell and one of its primary functions appears to be the augmentation of its cytoplasmic apparatus for synthesis and storage of lysosomal granules. The macrophage and the epithelioid cell are different forms of the same cell. This concept differs from that of many tissue culturists who contend that the mature lymphocyte can transform into a monocytoid cell, histiocyte and macrophage.

In summary, the theme of the conference was how cultured cells or tissues related to in-vivo progenitors, and how genetic systems may alter the activity of cells in vitro.

The monograph should be on the reference shelf of those working in the field of tissue culture.

E. M. Schleicher, Ph.D.
Minneapolis, Minnesota



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Contraindications: Dextro-amphetamine sulfate: In hyperexcitability and in agitated prepsychotic states. Previous allergic or idiosyncratic reactions to meprobamate.
Precautions: Use with caution in patients hypersensitive to sympathomimetic compounds, who have coronary or cardiovascular disease, or are severely hypertensive.

Dextro-amphetamine sulfate: Excessive use by unstable individuals may result in psychological dependence.

Meprobamate: Careful supervision of dose and amounts prescribed is advised, especially for patients with known propensity for taking excessive quantities of drugs. Excessive and prolonged use in susceptible persons, e.g. alcoholics, former addicts, and other severe psychoneurotics, has been reported to result in dependence on the drug. Where excessive dosage has continued for weeks or months, reduce dosage gradually. Sudden withdrawal may precipitate recurrence of preexisting symptoms such as anxiety, anorexia, or insomnia; or withdrawal reactions such as vomiting, ataxia, tremors, muscle twitching and, rarely, epileptiform seizures. Should meprobamate cause drowsiness or visual disturbances, reduce dosage and avoid operation of motor vehicles, machinery or other activity requiring alertness. Effects of excessive alcohol consumption may be increased by meprobamate. Appropriate caution is recommended with patients prone to excessive drinking. In patients prone to both petit and grand mal epilepsy meprobamate may precipitate grand mal attacks. Prescribe cautiously and in small quantities to patients with suicidal tendencies.
Side Effects: Overstimulation of the central nervous system, jitteriness and insomnia or drowsiness. Dextro-amphetamine sulfate: Insomnia, excitability, and increased motor activity are common and ordinarily mild side effects. Confusion, anxiety, aggressiveness, increased libido, and hallucinations have also been observed, especially in mentally ill patients. Rebound fatigue and depression may follow central stimulation. Other effects may include dry mouth, anorexia, nausea, vomiting, diarrhea, and increased cardiovascular reactivity.

Meprobamate: Drowsiness may occur and can be associated with ataxia; the symptom can usually be controlled by decreasing the dose, or by concomitant administration of central stimulants. Allergic or idiosyncratic reactions: maculopapular rash, acute nonthrombocytopenic purpura with petechiae, ecchymoses, peripheral edema and fever, transient leukopenia. A case of fatal bullous dermatitis, following administration of meprobamate and prednisolone, has been reported. Hypersensitivity has produced fever, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, stomatitis, proctitis (1 case), anaphylaxis, agranulocytosis and thrombocytopenic purpura, and a fatal instance of aplastic anemia, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity, usually after excessive dosage. Impairment of visual accommodation. Massive overdosage may produce drowsiness, lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse.

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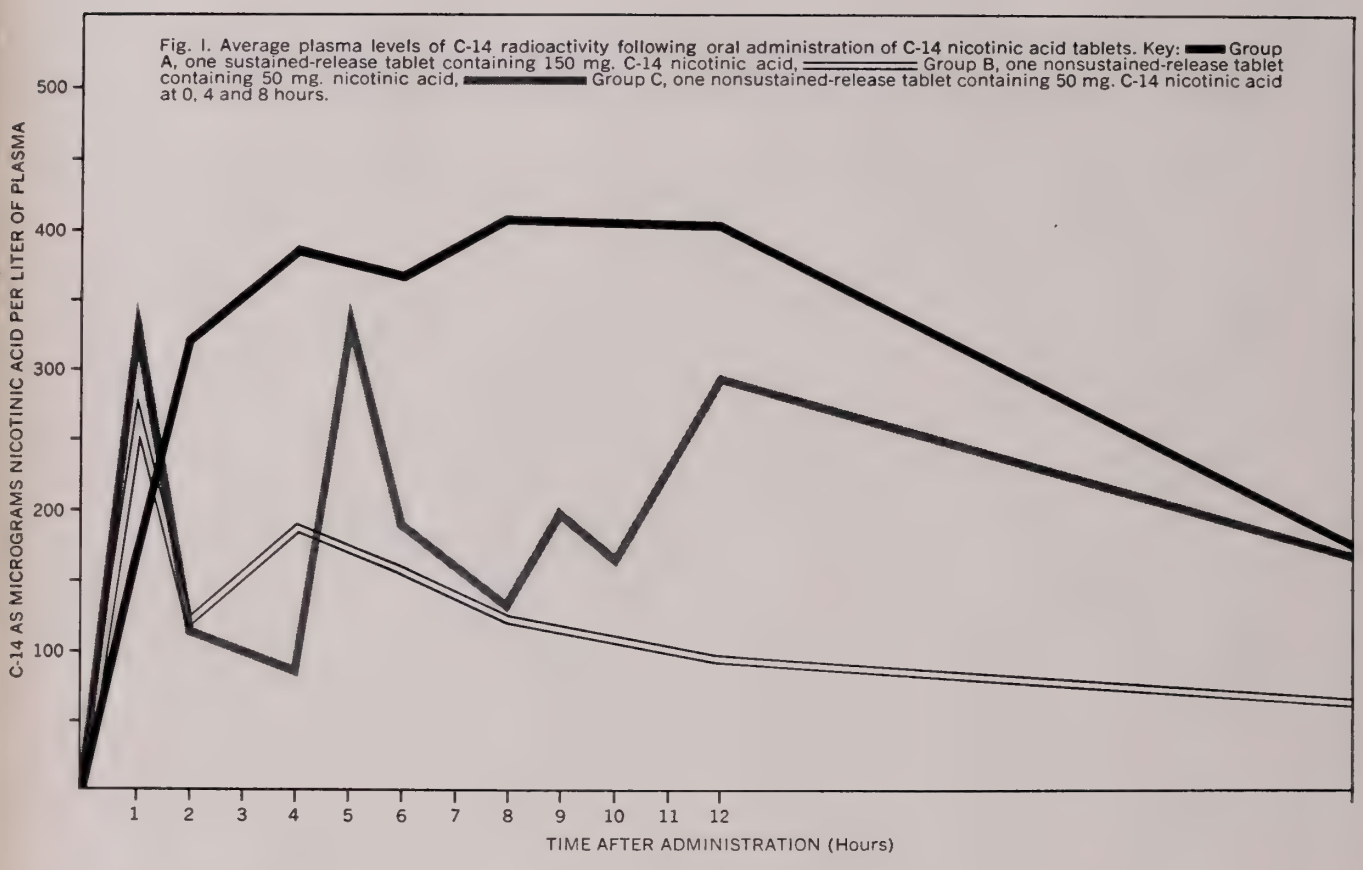
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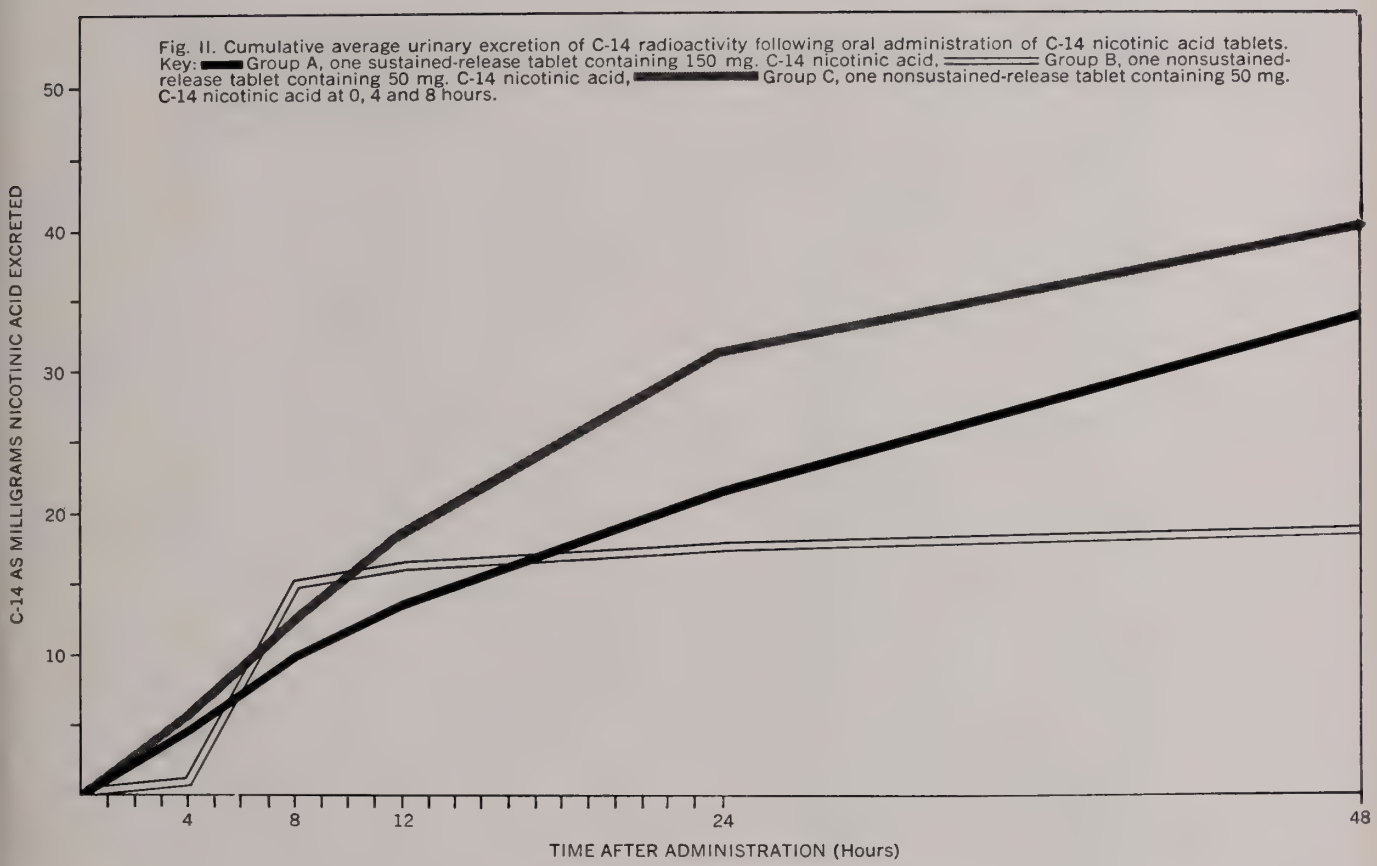
Human volunteer subjects were administered Geroniazol TT tablets with the nicotinic acid component made radioactive with C-14. Plasma and urine samples were analyzed. (See Figures I and II) The radioactive tracer study substantiated the previous clinical evidence that the release of nicotinic acid from the Geroniazol TT tablet produced a gradual rise in plasma levels to a plateau for a total of 12 hours and more.

Such proven sustained activity makes the management of geriatric patients much easier by minimizing the possibility of neglected doses through absent-mindedness or senile confusion. Therapy *can* be continuous on a daily dose of only one Geroniazol TT tablet every 12 hours.

The gradual release of nicotinic acid in Geroniazol TT will provide the well-known peripheral vasodilatation needed in patients with deficient circulation and with a minimum amount (if any) of "flushing." Also, cerebrovascular circulation is complemented by pentylenetetrazol, long-established as a cerebral and respiratory stimulant.

Geroniazol TT improves the typical, unfortunate, signs of senile confusion. Patients become more alert,

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Contraindications: There are no known contraindications.

Precautions: Exercise caution when treating patients with a low convulsive threshold.

Side Effects: Side effects are rarely encountered, however due to the vasodilatation effect of nicotinic acid, transitory mild nausea, flushing, tingling and pruritus are possible.

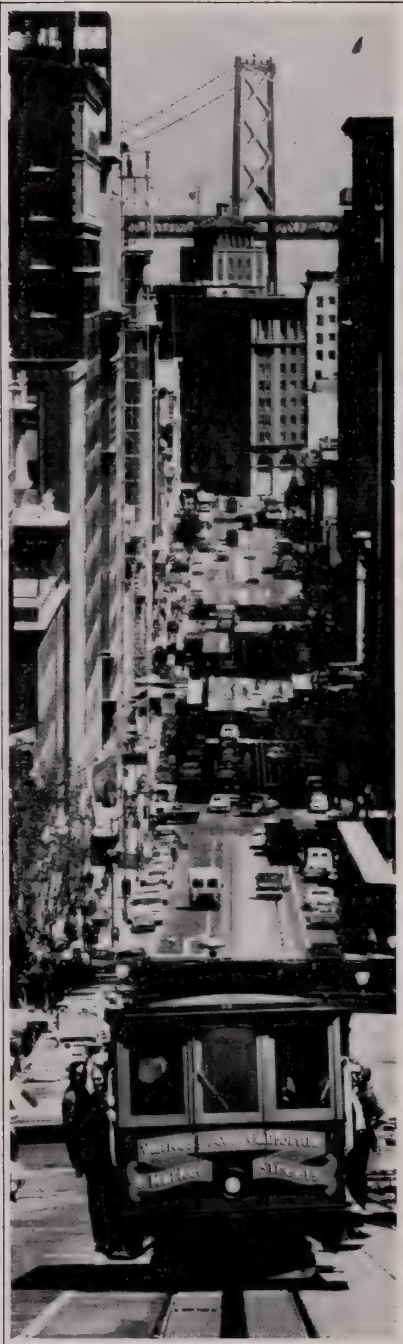
Dosage: One tablet every 12 hours.

Supplied: Prescribe bottles of 100 tablets, to take advantage of recent price reduction.

References: 1. Report by Nuclear Science & Engineering Corp., Pittsburgh, Pa., in files of Philips Roxane Laboratories. 2. Connolly, R.: W. Virginia Med. J. *56*:263 (Aug.) 1960. 3. Curran, T. R., and Phelps, D. K.: Am. Pract. & Digest Treat. *11*:617 (July) 1960.

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SAN FRANCISCO, CALIFORNIA · JUNE 16-20, 1968

AMERICAN MEDICAL ASSOCIATION'S 117th ANNUAL CONVENTION · BROOKS HALL



Meetings and Announcements

That man proves his worth who can make us listen when he is by, and think when he has gone.—Comtesse Diane

MAY

Zumbro Valley Medical Society, May 1, Regular Meeting, Plummer Hall, 7:00 P.M.

Southwestern Minnesota Medical Society, May 6, Ehlers Supper Club, 7:00 P.M.

Scott-Carver County Medical Society, May 7, Wagner Supper Club, Jordan, 7:30 P.M.

Minnesota Academy of Medicine, May 8, Town and Country Club, St. Paul, 7:00 P.M.

Camp Release District Medical Society Monthly Meeting, Hunt Hotel, Montevideo, 7:30 P.M., May 9.

St. Louis County Medical Society, May 9, Executive Committee, St. Mary's Hospital, 6:00 P.M., Regular Meeting, St. Mary's Hospital, 8:00 P.M.

Hennepin County Medical Society joint meeting with Minneapolis Surgical Society, Minneapolis Pediatric Society, Hennepin County Academy of General Practice, & Hennepin County Psychiatric Society, May 13.

Minnesota Chapter, American Academy of Pediatrics Chapter Meeting, Kahler Hotel, Rochester, Noon, May 14.

West Central Minnesota Medical Society Regular Meeting with speaker, Morris, 8:00 P.M., May 14.

Blue Earth Valley Medical Society Regular Meeting, Interlaken Golf Club, Fairmont, May 15, 7:00 P.M.

Kandiyohi-Swift-Meeker County Medical Society, May 16, Westwood Inn, Spicer, 7:00 P.M.

McLeod County Medical Society, May 16.

Minnesota Society of Internal Medicine, May 18, St. Luke's Hospital, Duluth, Registration 8:00 A.M.

Steele County Medical Society, May 21, Inntown Motel, Owatonna, 6:30 P.M.

Minnesota Surgical Society, May 24, Rochester.

Blue Earth County Medical Society, May 27, 8:00 P.M.

Range County Medical Society General and Executive Meeting, 7:00 P.M. dinner meeting, in Virginia or Grand Rapids, May 28.

Minnesota Academy of Ophthalmology and Otolaryngology, Rochester. (Date and time to be announced.)

JUNE

Nicollet-LeSueur County Medical Society, June 3, Holiday House, 6:30 P.M.

Southwestern Minnesota Medical Society, June 3, Ehlers Supper Club, 7:00 P.M.

Scott-Carver County Medical Society, June 4, New Prague Country Club, 7:30 P.M.

St. Louis County Medical Society Executive Committee, St. Luke's Hospital, June 13, 6:00 P.M.—Regular Meeting, St. Luke's Hospital, 8:00 P.M.

Kandiyohi-Swift-Meeker County Medical Society, June 20, Litchfield Country Club, 5:00 P.M.

McLeod County Medical Society, June 20

The Minnesota Thoracic Society and the Minnesota Respiratory Health Association announce a second award contest for medical students, interns and resident physicians in Minnesota.

(A) An award of $200.00 is offered for the best paper submitted by a senior medical student or intern on some aspect of respiratory disease, preferably based upon laboratory or clinical investigation.

(B) An award of $300.00 is offered for the best paper submitted by a resident physician based upon clinical or laboratory investigation in the area of respiratory disease.

Further information may be obtained from the Secretary. Entries should be submitted by September 1, 1968 to: David E. Dines, M.D., Secretary, Minnesota Thoracic Society, Mayo Clinic, Rochester, Minnesota.

Guest Speaker—Dr. Denton Cooley

Annual meeting of the Minnesota Chapter of the American College of Chest Physicians, May 14, 1968 in Plummer Hall, Mayo Clinic, Rochester. Dinner will precede the meeting which will start at 8:00 p.m. Guest speaker for the evening will be Dr. Denton Cooley. His talk will be "Surgical Treatment of Thoracic Aneurysms, Indications, Special Problems and Results." Everyone is invited. Contact: Dr. Drew Miller of the Mayo Clinic.

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Special Article

Suicide*

The Nondiminishing Rate

RONALD MARIS**
Hanover, New Hampshire

WE ARE NOT preventing suicide in the United States. In 1960 the suicide rate in the U. S. was about 11 per 100,000 population, almost exactly the same as in 1900. During those 60 years life expectancy has increased from about 35 to 70 years. Death from scarlet fever, typhoid fever, measles, diphtheria, and whooping cough has been virtually eliminated; death from tuberculosis and pneumonia are less than one-fifth as frequent as they were in 1900. Death by nephritis has been halved. Generally, the crude death rate has decreased from 17.2 per 1,000 population to 9.6 from 1900 to 1960.

All this means that suicide is becoming an increasingly important factor in the death rate. In fact, if future generations want to lower the death rate they are well-advised to focus on the prevention of suicide and accidents, not on so-called natural deaths. Most of us do not want to live much beyond 70 years, but we are concerned about unnecessary, premature death. There is considerable evidence to suggest that accidents and suicide have much in common: that they spring from common causes. Indeed, many accidents are probably disguised suicides. There is evidence that not only has suicide failed to decrease over the years but that, especially in some groups, it has actually increased. The Metropolitan Life Insurance Company discloses that in the last 10 years the suicide rate has increased 10 percent among white males in the U. S., but 33 percent among non-white males. The corresponding figures for females are 49 and 80 percent. These changes are primarily the result of higher suicide rates among younger persons, ages 15-24.

The Ambivalence of a Suicide

Suicides are notoriously ambivalent about dying, which raises the interesting possibility of our *right* to simply respond to the life-affirming side of their motivation, rather than the life-denying side.

A few years ago a member of my doctoral examination committee asked me in all seriousness if I really thought that suicide was a social problem. "After all," he said, "It's still true that the typical suicide is an old, white male, who is single and usually in poor health, often alcoholic. Given the present population explosion would not the world be better off without these people?" I suspect that many of us feel the same way. Certainly in your work as physicians you must ask yourselves periodically, whether some people should not be allowed to die, especially in the case of clearly terminal illnesses which are painful and expensive.

The Right to Die

There is the further question whether or not people have the right to terminate their life, since it is their life. Philosophers David Hume and Bertrand Russell have both defended this right. In fact, one way of transcending death is to elect it, rather than let it eat away at you. Surrender can be victory! Life alone is not our goal, but life with purpose and quality. Nobel prize-winning physicist, Percy Bridgman, killed himself and left this note: "My work is over, why wait?" Since the suicide rate for men is highest at retirement age, I suspect that many of us can

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*Presented to the staff of the Fairview Hospital, Minneapolis, Minnesota, in December of 1967. Readers who wish references and tables are encouraged to write the author for another manuscript in which the problem of preventing suicide is given a more scholarly treatment.

**Assistant Professor, Dartmouth College, Hanover.

sympathize with Bridgman's logic.

The Right to Reconsider

Suicide prevention centers are possible because we believe that potential suicides have the right, indeed the obligation, to reconsider suicide under less agitated and confused circumstances. The rights of the relatives and associates of the suicide have to be weighed; for example, does not his wife have the right to his support and companionship? Don't his children have the right to escape the social stigma of being labeled by their schoolmates as children of a suicide?

Suicide vs. Homicide

Let me suggest that we should be ambivalent about suicide because the suicide rate and the homicide rate often are inversely related. I know of few populations in which it has been possible to reduce both rates simultaneously. This suggests that to prevent suicide is to cause homicide and lesser acts of aggression. (In fact Menninger called suicide "Murder-in-the-hundred-and-eightieth-degree.") Is not suicide to be preferred to homicide? I sometimes justify my killing deer on the grounds that it keeps me from killing myself. This reasoning is not as far-fetched as it may seem. It is a fact that a nation's suicide rate always drops sharply during engagement in an international war. We also know that Negroes have very low suicide rates, but that their homicide and assault rates are very high. All of which makes me wonder if suicide rates have remained high in part because we want them to.

Suicidal Warnings

Seventy-five percent of all suicides have seen a physician within four months prior to their death. Thus, if doctors were sensitized to suicidal warnings and made referrals to the psychiatric unit or local prevention centers, the suicide rate could probably be lowered significantly.

Alcoholic or Depressed

A study in St. Louis showed that 75 percent of all suicides were either depressed or alcoholic or both (Menninger felt that alcoholism was a suicidal equivalent). Further, potential suicides do communicate their intention to kill themselves; in fact, 80 percent of all suicides have made a previous unsuccessful attempt. This means that four out of five gave dramatic warning of their intent to kill themselves. Usually, when the probability of suicide is high, the person will have a definite plan of action (the more specific the plan, the higher the lethality). Often, just before the act, appetite falls off, sexual activity diminishes, insomnia is present, a will may be drawn up, and previously valued possessions may be given away.

Social Factors

Certain types of people are more prone to suicide than others. The most common suicide is 50 to 70 years old, white, male, unmarried, and of a lower social class.

Personality Types

The French sociologist, Emile Durkheim, has argued that socially suicides are disproportionately isolated ("egoistic") and unregulated ("anomic"): living in a social environment of relative normlessness: without external restraint. In my Chicago research, I found a high negative correlation between the suicide rate and population per household, controlling for other relevant variables.

Studies of case histories reveal that, as children, suicides were often subjected to high parental severity while they were dependent upon others and dared not agress against them. They also tended to be normative virtuosos, unable to deviate from internalized role expectations; this inflexibility led to an inability to deal adequately with failure; to justify their actual performances; to shift their goals. They were easily shamed and showed high levels of guilt and hopelessness.

Preventive Programs

Not only has there been too little response to the cry for help, but much of the action undertaken has been misguided and premature: misguided in the sense that the programs were clearly not directed towards those with a high probability of suicide, but rather toward relatively minor, non-suicidal crisis situations. Premature in the sense that huge sums of federal money have been poured into unrewarding pro-

grams initiated without the guidance of solid, basic research.

The Prevention Center vs. The Morgue

The suicide prevention center in Chicago tended to see manic, young, married females (i.e., low lethality cases), while the coroner saw depressed, old, unmarried males. Clearly, the persons elevating the suicide rate are not contacting the suicide prevention center. Something is fundamentally wrong with the suicide prevention program. For example, why use a telephone as the major instrument of contact? Does it make any sense to expect a 65-year-old male who is depressed and hopeless (i.e., who wants to die) to pick up the telephone and pour out his soul to some young, female volunteer? Emphatically not.

Basic Research

If we are ever going to prevent suicide, basic research is the only answer. First, we must be clear on the nature and types of suicide. Grasp of the principles of completed suicides must precede design of prevention programs. Also, experiments must be conducted with control groups! Although it is always a moral problem to design an experiment which exempts some human beings from treatment while treating others, we have little to lose, since present programs have largely been failures anyway. Once successful intervention programs have been devised, the scope of treatment can be generalized.

Nonprofessional Management

Another reason for prior failure is that nonprofessional religious groups have initiated much of the suicide prevention movement (e.g., The Samaritans in London and Rescue Incorporated in Boston). In spite of their good intentions, ministers are not qualified to manage suicide prevention centers alone. Psychologists, psychiatrists, M.D.'s, and sociologists are needed.

Warning Signs

Acute and Chronic Suicides

There are different types of suicide; some are easier to prevent than others.

An acute situation might exist for a 29-year-old woman whose grandmother and mother both suicided on their 30th birthdays. Chances are good that the young woman will be all right, if you can get her past her 30th birthday. Other persons may have a style of life, physical or psychological attributes, that continually goad them to try suicide until they finally succeed. Marital problems, physical deformities, mental illness can all lead to chronic attempts. Remember that 80 percent of all suicides have tried suicide at least once before, and they often succeed just when they seem to be improving: when they regain the energy needed to kill themselves. One of the most dangerous times is the three-month period immediately following the beginning of improvement after a depression.

Appeal vs. Ordeal Suicides

We can also distinguish between "appeal" suicides and "ordeal" suicides. Many women attempt suicide as an ultimate appeal to their husbands to improve an unhappy marital relationship. If the appeal is successful, the possibility of future suicide is lessened considerably. On the other hand, the prognosis is not good for a man who is undergoing the ordeal of growing old, living alone, feeling ill more often than well, being unable to work, etc.

Ecological Groups

Once the profile of high-risk groups has been drawn, it is reasonable to assume that mass intervention programs might be aimed at certain ecological groups. For example, the areas with the highest suicide rates in Chicago are in skid-row areas (Madison & Halsted area) and on North Michigan Avenue. Perhaps social workers could invade these areas and institute measures aimed at minimizing social isolation and anomy.* The basic change from present suicide prevention center programs would be the decentralization and invasion of services. Communities with low suicide rates are usually populated by religious fundamentalists, have highly legalistic and authoritarian government, are extremely poor and uneducated (says Durkheim), and have high rates of assault and homicide. On the other hand, communities with high suicide rates include many of the nation's outstanding cities: viz., Berkeley, San Francisco, Los Angeles, Miami, Denver, Seattle, and St. Louis (Minneapolis is 13.5/100,000; just

*See Test Your Word Score Page 649.

above the mean). Maybe we simply cannot have our cake and eat it too.

Communication Channels

Another key question would be what communication channels might be open to the high-risk group, besides the telephone. Perhaps television, bars, and liquor stores, could be utilized.

Comments

We should consider a control dilemma of major proportions. I am not sure that most of us would want to live in the kind of community which would minimize suicide. Perhaps a high suicide rate is one of the necessary costs of a certain style of life, of a certain level of civilization.

In Aldous Huxley's classic work, *Brave New World*, a world very much like what ours is becoming, suicide was unheard of, even inconceivable. In the closing pages of the book the savage, an Indian brought into the Brave New World, wonders if happiness is the end of life; if the completely comfortable life is worth living:

"What you need," the savage went on, "is something with tears for a change. Nothing costs enough here . . . exposing what is mortal and unsure to all that fortune and death dare, even for an eggshell. Isn't there something in that?" he asked, looking up at Mustapha Mond (a world controller). "Quite apart from God—though of course God would be a reason for it. Isn't there something in living dangerously?"

"There's a great deal in it," the controller replied. "Men and women must have their adrenals stimulated from time to time."

"What?" questioned the savage, uncomprehending.

"It's one of the conditions of perfect health. That's why we have made the V.P.S. treatments compulsory."

"V.P.S.?"

"Violent passion surrogate. Regularly once a month. We flood the whole system with adrenin. It's the complete physiological equivalent of fear and rage. All the tonic effects of murdering Desdemona and being murdered by Othello, without any of the inconveniences."

"But I like the inconveniences."

"We don't," said the controller. "We prefer to do things comfortably."

"But I don't want comfort. I want God, I want poetry, I want real danger, I want freedom, I want goodness, I want sin."

"In fact," said Mustapha Mond, "you're claiming the right to be unhappy."

"Not to mention the right to grow old and ugly and impotent; the right to have syphilis and cancer; the right to have too little to eat; the right to be lousy; the right to live in constant apprehension of what may happen tomorrow; the right to catch typhoid; the right to be tortured by unspeakable pains of every kind."

There was a long silence.

"I claim them all," said the savage at last.

So this is where we stand. We are not preventing suicide, because we are ambivalent about its worth, insensitive to its symptoms, too ready to act on an incomplete understanding of it, and thus unable to control it. I close by asking you: Is this a sorry state of affairs or not? Should suicide be prevented and how? Or should men have the right to be unhappy and to end their own lives? And perhaps most importantly, can we preserve the right to be unhappy and at the same time prevent suicide?

Minnesota Medicine Cover Photographs

In order to encourage more physicians to submit color slides for use on the cover of MINNESOTA MEDICINE the competition is being discontinued. The picture editor now invites all physician-photographers to send 35 mm. color slides of suitable subjects for consideration as cover pictures. The format must be horizontal because of printing limitations. Pictures high-lighting Minnesota seasons, places, and activities will have an automatic advantage. No limit as to the number of slides sent will be set, but all slides should be individually identified. All slides will be returned. Physicians whose pictures are used as covers will be recognized in MINNESOTA MEDICINE. We can use many more pictures than we have received in the past.

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Prescribing information on next page.

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DECLOMYCIN Demethylchlortetracycline should be equally or more effective therapeutically than other tetracyclines when the offending organisms are tetracycline-sensitive.

Contraindication: History of hypersensitivity to demethylchlortetracycline.

Warning—In renal impairment, usual doses may lead to excessive accumulation and liver toxicity. Under such conditions, lower than usual doses are indicated, and, if therapy is prolonged, serum level determinations may be advisable. A photodynamic reaction to natural or artificial sunlight has been observed. Small amounts of drug and short exposure may produce an exaggerated sunburn reaction which may range from erythema to severe skin manifestations. In a smaller proportion, photoallergic reactions have been reported. Patients should avoid direct exposure to sunlight and discontinue drug at the first evidence of skin discomfort. Necessary subsequent courses of treatment with tetracyclines should be carefully observed.

Precautions—Overgrowth of nonsusceptible organisms may occur. Constant observation is essential. If new infections appear, appropriate measures should be taken. In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment.

Side Effects—Gastrointestinal system—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin—maculopapular and erythematous rashes; a rare case of exfoliative dermatitis has been reported. Photosensitivity; onycholysis and discoloration of the nails (rare). Kidney—rise in BUN, apparently dose related. Transient increase in urinary output, sometimes accompanied by thirst (rare). Hypersensitivity reactions—urticaria, angioneurotic edema, anaphylaxis. Teeth—dental staining (yellow-brown) in children of mothers given this drug during the latter half of pregnancy, and in children given the drug during the neonatal period, infancy and early childhood. Enamel hypoplasia has been seen in a few children. If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy.

Average Adult Daily Dosage: 150 mg q.i.d. or 300 mg b.i.d. Should be given 1 hour before or 2 hours after meals, since absorption is impaired by the concomitant administration of high calcium content drugs, foods and some dairy products. Treatment of streptococcal infections should continue for 10 days, even though symptoms have subsided.

In the treatment of syphilis a dosage schedule of a total of 12 to 18 Gm given in equally divided doses over a period of 10 to 15 days should be followed. Close follow-up observation of the patient is recommended, including appropriate laboratory tests, since demethylchlortetracycline has not had adequate evaluation in all stages of syphilis. Spinal fluid examination should be included as part of this follow-up.

Acute gonococcal anterior urethritis in males has been treated effectively with a single dose of 600-900 mg of DECLOMYCIN Demethylchlortetracycline. Individuals unable to tolerate large single doses due to gastrointestinal side effects may be treated with 150 mg every 6 hours for a minimum of 4 doses or 300 mg every 12 hours for a minimum of 2 doses. Females should be treated with a dosage of 150 mg every 6 hours or 300 mg every 12 hours until a cure is effected.

Primary Atypical Pneumonia (Eaton Agent): The average adult daily dosage is 900 mg in 3 divided doses for six days.

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Law and Medicine

Today's Top Malpractice Risks*

(1) The author reviewed 1000 Malpractice Claims. Many doctors are not aware of the recent trends that have made certain risks today's top malpractice threats.

Three specific faults present the greatest malpractice dangers: (1) inadequate medical records; (2) colleagues' and assistants' mistakes; (3) errors in diagnostic tests. Court awards are rising steeply, especially for deaths of children and housewives. Malpractice experts with whom the author conferred agreed that if all private practitioners would take steps to minimize these three risks, the current incidence of malpractice claims would drop shortly. Four types of faulty record-keeping are recorded. (1) Surgeons invite trouble when they fail to keep adequate records of surgical operations in detail, fail to record complications and bad results, or fail to record the condition of the patient before, during, and after surgery. The Alaska Supreme Court stressed the importance of precise records; when lacking, surgeons face the jury with res ipsa loquitur (the thing speaks for itself). The case in point was a patient who suffered a division of a recurrent laryngeal nerve during a routine subtotal thyroidectomy. The operative report was so sketchy that an expert medical witness could not give an exact opinion on negligence. The Supreme Court ruled that the patient did not need any more proof of negligence.

The effect of the Alaska Supreme Court ruling has been felt in other jurisdictions. It led to a recent $48,500 settlement, paid to a man who lost his right kidney because of a surgical mishap. In separating multiple adhesions, the right ureter was divided. Defense experts agreed that the operative slip alone did not constitute malpractice. The operative report was not dictated until three weeks after surgery and did not mention either the adhesions or their location. The judge stated he was sending the $150,000 claim to the jury; but it was promptly settled out of court.

Astute trial lawyers make it a point to compare the date of surgery with the date of the dictation of the report.

(2) Failure to make a record of allergy. A four-man medical group paid $116,000 settlement for a death because one of its members was guilty of a fatal omission. A nurse, in the doctor's presence, gave an injection of penicillin. The patient had a reaction but was able to leave the office. The doctor was urgently called away and forgot to record the reaction. Months later the same patient came to the same office with a sore throat. Another doctor of the group checked the record and ordered penicillin. The patient died within an hour of the injection. A New York malpractice attorney states that anyone who does not record allergic reactions is exposing himself to a lawsuit, as no doctor can remember the peculiarities of all his patients. Records are even more necessary when treatment is given by a partner, a colleague or a hospital physician who may be ignorant of a known reaction.

An instructor was away lecturing to his class on allergy. A patient who he knew was sensitive to aspirin was waiting to see him at his office. A nurse gave the patient a small dose of aspirin. The treatment proved fatal.

*John H. Tovey, J. D. Medical Economics—July 10, 1967. In 4 parts.

Fortunately the family did not sue.

(3) Failure to report negative findings. A judge advised a doctor to settle a claim for $4,000. An expert witness had stated that a stillborn child should have been delivered by cesarean section. The doctor insisted that he thought the patient could deliver the child normally despite a small pelvis. The plaintiff's lawyer asked the $64 question: "Look at your records and tell me how small the pelvis is." The doctor couldn't because he had no record of any measurements. As advised by the judge, a settlement was negotiated.

Melvin Belli, the California trial expert, states: "If a doctor fails to record negative findings he'll be hard pressed to prove to a jury that he did the examination, or ordered the test in question." Belli's words are given substance by a settlement for $25,000 of a case against an internist which took every penny he had. There were no records of allergy or other tests. The doctor said the tests were negative, why write them down and waste ink.

(4) Failure to record significant phone conversations. Malpractice lawyers have for years warned against giving phone consultations. If a doctor does give one, he should make detailed notes of treatment and medications prescribed. A doctor had a lawsuit brought against him because of a brain-damaged infant. The fatality was the result of an over-dose of medicine, the result of a mistaken phone order. The pharmacist swore he typed the label calling for an adult dose as the doctor instructed. The doctor swore he did not so order. Since the physician had no record of the conversation, his insurance carrier decided to settle.

An internist, on the phone, advised on the care of a 16-year-old boy with abdominal pain, without suggesting a personal visit or hospitalization. The boy died of a ruptured appendix and peritonitis. The mother sued for $100,000. She swore that she told the doctor her son had abdominal pain, elevated temperature and abdominal tenderness The doctor remembered none of this and had no record. He stated that if symptoms had indicated an emergency, he would have responded. A settlement was made for $18,000.

Note: During the years the science of medicine has advanced and so has the practice of law.

I can recall when malpractice insurance for $5,000 to $25,000 was considered adequate. The annual premium was about $25.00. At present those amounts of insurance are no longer adequate in view of the growing generosity of the courts.

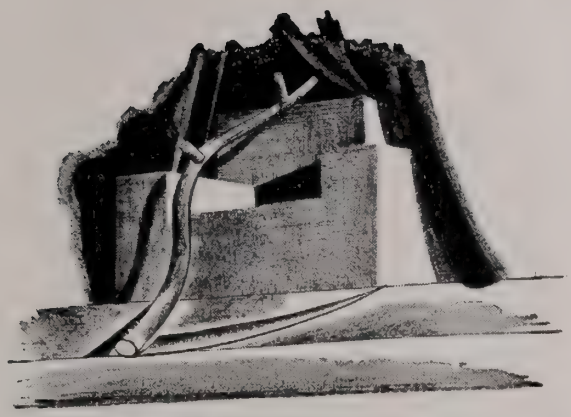
Stanley R. Maxeiner, Sr., M.D.
Minneapolis, Minnesota

The Question

At some time in life every man has what is commonly called "a chance." The question is *not,* what *is* that chance, but *what will he do with it?* There are few questions in this life to which the solution is more important to each puzzled mortal than that which applies to *man's life,* from its first sleep in the cradle, *what will he do with it?*—E. Bulwer Lytton

---

I prefer the wicked rather than the foolish; the wicked sometimes rest.—Alexandre Dumas (pere)



In Memoriam

Our life contains a thousand springs,
And dies if one be gone;
Strange that a harp of thousand strings
Should keep in tune so long.—Watts

JOHN K. GROTTING, M.D.

Dr. John Grotting, 52, widely-known Minneapolis plastic surgeon, died February 8. A native of Minneapolis, he received his medical degree from the University of Minnesota and after interning a year in Receiving Hospital at Detroit, Michigan, he became a fellow at the Mayo Clinic in Rochester.

He was a member of the American Society of Plastic Surgeons, American Medical Association, Hennepin County Medical Society, Minnesota State Medical Association, Minnesota Surgical Society and the Mayo Alumni Association. He also was a fellow of the American College of Surgeons and a diplomate of the American Board of Plastic Surgeons.

He is survived by his wife, four sons and a daughter.

WILLIAM D. BROWN, SR., M.D.

Dr William D. Brown, Sr., 65, Minneapolis physician for forty years, died March 19. He graduated from Central High School and attended the University of Minnesota where he received his medical degree in 1925.

Dr. Brown was an active member of the National Association for the Advancement of Colored People and also a member of the American Medical Association, Hennepin County Medical Society and the Minnesota State Medical Association.

He is survived by his wife and a son, Dr. William Brown, Jr. of Minneapolis.

JOSEPH D. WALLER, M.D.

Dr. Joseph D. Waller, 86, Pine City ophthalmologist, died January 6. He was born in Litchfield and attended the University of Minnesota where he obtained his medical degree in 1905.

He was a member of the East Central Medical Society, the American Medical Association and was a 50 Club and Associate Member of the Minnesota State Medical Association.

He is survived by his wife.

MARTIN NORDLAND, M.D.

Dr. Martin Nordland, 79, Minneapolis surgeon, died March 23. He specialized in thyroid surgery and was listed in "Who's Who in America."

A native of Austin, Minnesota, he received his medical degree from the University of Minnesota in 1911 and was a member of the faculty in the Department of Surgery at the University of Minnesota. Dr. Nordland was chief of staff at Northwestern Hospital in 1931 and 1932, a member of the founders' group of the American Board of Surgery and in 1934 and 1935 was president of the Minneapolis Surgical Society.

He was a former associate editor of LANCET, a former vice-president of the Hennepin County Medical Society, a member of the American Medical Association and a Life and 50 Club Member of the Minnesota State Medical Association.

He is survived by his wife and a daughter.

ROBERT SCHWYZER, M.D.

Dr. Robert Schwyzer, 77, former chief surgeon of the Kreisspital, Bulach, Switzerland, died following a prolonged illness October 28, 1967.

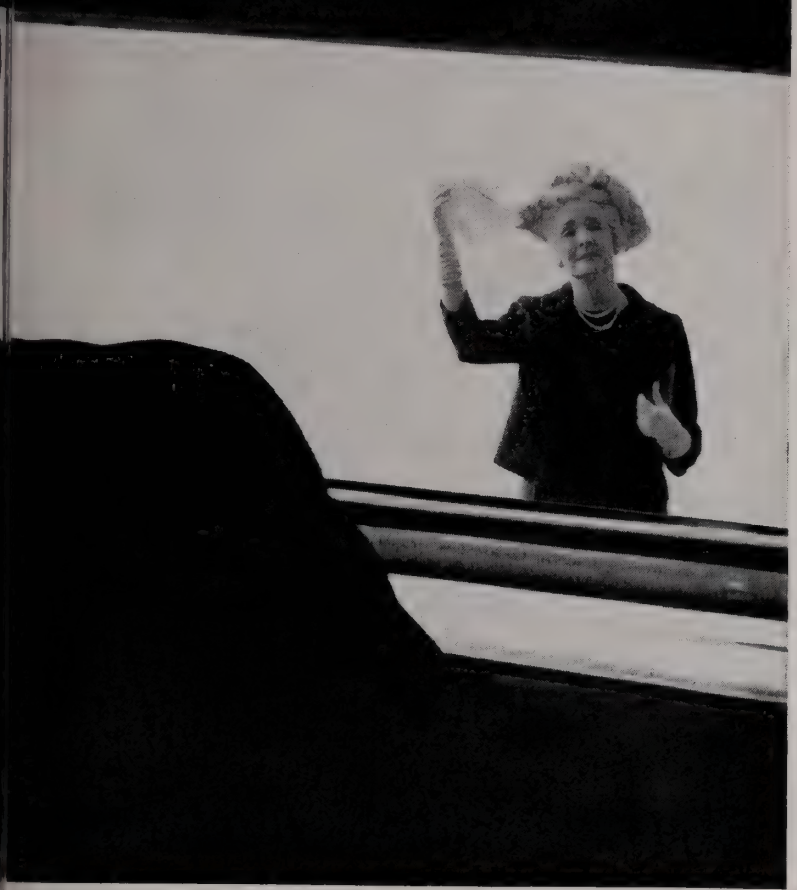
Dr. Robert Schwyzer, a relative of the late Dr. Arnold Schwyzer of St. Paul and Dr. Gustav Schwyzer of Minneapolis, received his training at the University of Zurich, Switzerland. He came to Minnesota and practiced medicine at Blackduck for two years transferring to Minneapolis in 1927 to become associated with Dr. Gustav Schwyzer and a member of the Hennepin County Medical Society. In 1932, he returned to Switzerland.

He is survived by his wife, a son and a daughter.



Indications: Tofrānil is recommended for the treatment of depressive states of diverse psychopathology.
Contraindications: The concomitant use of Tofrānil and monoamine oxidase inhibiting (M.A.O.I.) compounds is contraindicated. Hyperpyretic crises or severe convulsive seizures may occur. Potentiation of adverse effects can be serious or even fatal. An interval of at least 7 days after M.A.O.I. therapy has been discontinued should be allowed before Tofrānil may be substituted. Initial Tofrānil dosage should be low, increases should be gradual, and the patient's progress should be carefully observed.
Warning: Clinical reports have suggested that there may be a risk of teratogenesis associated with the use of this compound during the first trimester of pregnancy. Unless, in the opinion of the prescribing physician, the potential benefits outweigh the possible risks, Tofrānil should not be used during the first trimester of pregnancy.
Cardiovascular complications, including myocardial infarction and arrhythmias, have occasionally occurred in susceptible individuals. Patients with cardiovascular disease should be given the drug only under careful observation and in low dosage.
Precautions: Since suicide is always a possibility in severely depressed patients and one which may persist until significant remission occurs, such patients should be carefully supervised during early treatment with Tofrānil. Some severely depressed patients may also require hospitalization and/or concomitant electroconvulsive therapy.
Because of its anticholinergic effect, caution should be observed in prescribing Tofrānil for patients with increased intraocular pressure.
In rare instances, transient cardiac arrhythmias have occurred in hyperthyroid patients and in patients receiving thyroid medication when Tofrānil was added to the regimen.
Imipramine may block the pharmacologic activity of guanethidine and other related adrenergic neuron-blocking agents.
The drug is not recommended at the present time in patients under 12 years of age.
Adverse Reactions: Dryness of the mouth, tachycardia, constipation, disturbances of accommodation, sweating, dizziness, weight gain, urinary frequency or retention, nausea and vomiting, peripheral neuritis, mild parkinson-like syndrome, tremors, rare cases of falling in elderly patients, confusional states (with such symptoms as hallucinations and disorientation), activation of psychosis in schizophrenics and agitation (includ-

When a milestone in life is marred by depression...



Often in the mind of the lonely, widowed, depression-prone individual, she's not gaining a daughter...she's losing a son. The occasion may be marred by depression with such symptoms as feelings of sadness, incapacity, helplessness and hopelessness.

Tofrānil often relieves symptoms of depression.

As maintenance therapy during the active phase of depression, it may help prevent relapse.

The use of Tofrānil in patients receiving M.A.O.I.'s is contraindicated.

In patients with cardiovascular disease, hyperthyroidism or increased intraocular pressure; or in those receiving anticholinergics (including antiparkinsonism agents), thyroid medication, or antihypertensive adrenergic neuron-blocking agents; and in those in their first trimester of pregnancy, the special precautions listed in the prescribing information should be carefully observed.

Toxic reactions severe enough to require discontinuation of Tofrānil are uncommon. However, for complete details, please refer to the full prescribing information.

Tofrānil® imipramine hydrochloride Geigy

ing hypomanic and manic episodes) which may require dosage reduction and/or addition of a tranquilizer or temporary discontinuation of the drug, epileptiform seizures, orthostatic hypotension and substantial blood pressure fall in hypertensive patients, purpura, transient jaundice, bone marrow depression including agranulocytosis, sensitization and skin rash including photosensitization, eosinophilia, and mild withdrawal symptoms on sudden discontinuation after prolonged treatment with high doses. Occasional hormonal effects (impotence, decreased libido, and estrogenic effects) may be observed. Atropine-like effects may be more pronounced (e.g. paralytic ileus) in susceptible patients and in those using anticholinergic agents (including antiparkinsonism drugs).
Outpatient Adult Dosage: Initially, 75 mg. daily, increased, if necessary, to 150 or 200 mg. Maintenance dosage may be lower, 50 to 150 mg. daily, if possible.
Geriatric and Adolescent Dosage: Initially, 30 or 40 mg. daily, which may be increased according to response and tolerance. It is usually unnecessary to exceed 100 mg. daily.
A lag in therapeutic response, lasting from a few days to a few weeks, should be expected. When dosage recommendations are already being followed, increasing the dosage does not normally shorten this latency period and may increase the incidence of adverse reactions.
Availability: Tofrānil: Round tablets of 25 and 50 mg.; triangular tablets of 10 mg. for geriatric and adolescent use; and ampuls, each containing 25 mg. in 2 cc. for I.M. administration.
(B)46-850-C
For complete details, please refer to the full Prescribing Information.

Geigy Pharmaceuticals
Division of Geigy Chemical Corporation
Ardsley, New York 10502

TO-5522R

Annual Meeting

Rochester Will Host Our Annual Meeting



IT'S ANNUAL MEETING time in Rochester. In a setting of everything medical, the Minnesota State Medical Association will meet May 13, 14 and 15 for its 115th Annual Meeting. Members of the Zumbro Valley Medical Society will be the hosts for the 1968 event. Members of the Woman's Auxiliary will hold their 46th Annual Meeting in conjunction with the business and scientific sessions of the Association.

Business Sessions

The House of Delegates will meet for its opening session Sunday, May 12, at 2:00 P.M. in the Kahler Hotel. Delegates and interested physicians are advised to note the change in time for the second session of the House, which has been scheduled to convene Monday evening, May 15, at 7:30 P.M., a departure from its traditional Tuesday morning second session. Reference committees will meet at 8:00 P.M. Sunday to consider committee reports and resolutions. A second session of reference committee meetings will be scheduled, if needed, Monday morning at 9:30 A.M.

Because of the important role which the Reference Committee hearings and House of Delegates meetings play in determining future policy of the Association, the Council urges all members to attend these sessions and especially, the reference committee meetings where opinions of members will be welcomed.

Many of the nearly fifty scientific and nonscientific committees of the Association have scheduled 7:30 A.M. breakfast meetings Monday, Tuesday or Wednesday. Members of the committees are urged to attend their meetings and actively participate in matters scheduled for discussion and action.

Scientific and Technical Exhibits

The Committee on Scientific Assembly has

115th Annual Meeting

Program Timetable

Sunday, May 12

2:00 P.M.	House of Delegates—Kahler Hotel
6:00 P.M.	New Members, County Officers and Delegates Dinner—Kahler Hotel
8:00 P.M.	Reference Committees of the House of Delegates—Kahler Hotel

Monday, May 13

7:30 A.M.	Committee Breakfasts—Kahler Hotel
8:45 A.M.	Registration at Mayo Civic Auditorium— Exhibits open 8:45 a.m. to 5:00 p.m.
9:00 A.M.	Morning scientific session begins—Mayo Civic Auditorium
9:30 A.M.	Reference Committee Meetings—(If needed)—Kahler Hotel
12:15 P.M.	Round Table Luncheons—Kahler Hotel
2:00 P.M.	Afternoon scientific session begins—Mayo Civic Auditorium
7:30 P.M.	House of Delegates—Kahler Hotel
7:30 P.M.	Bridge Tournament—Holiday Inn

Tuesday, May 14

7:30 A.M.	Committee Breakfasts—Kahler Hotel
8:45 A.M.	Registration at Mayo Civic Auditorium— Exhibits open 8:45 a.m. to 5:00 p.m.
9:00 A.M.	Morning scientific session begins—Mayo Civic Auditorium
12:15 P.M.	Round Table Luncheons—Kahler Hotel
2:00 P.M.	Afternoon scientific session begins—Mayo Civic Auditorium
7:00 P.M.	Annual Banquet—Kahler Hotel—Preceded by reception at 6:00 p.m.

Wednesday, May 15

7:30 A.M.	Committee Breakfasts—Kahler Hotel
8:45 A.M.	Registration at Mayo Civic Auditorium— Exhibits open 8:45 a.m. to 12:00 p.m.
9:00 A.M.	Morning scientific session begins—Mayo Civic Auditorium
	End of meeting—12:00 p.m.

indicated that this year's scientific and technical exhibits in the Mayo Civic Auditorium will be particularly outstanding. Ample time will be provided before and between scientific sessions to view these fine exhibits.

The committee expresses the hope that physicians will make a point of indicating their appreciation to the technical exhibitors whose participation continues to help make the splendid scientific sessions possible.

Heart, Blood, Bones, Shock, Sex

The new "in depth" scientific program format promises to appeal to all physicians, regardless of medical specialty.

Major topics selected for presentation during the two and one half day scientific program include Heart, Blood, Bones, Shock and Sex. Program participants will include outstanding Minnesota physicians as well as a number of visiting experts. All scientific sessions will be at 9:00 A.M., and will be held in the Mayo Civic Auditorium. A listing of scientific sessions and participants appears at the close of this article. For more details, physicians are urged to consult the official Minnesota State Medical Association Annual Meeting program, which will be mailed to the membership.

Round Table Luncheons

A provocative and informative series of Round Table Luncheons have been scheduled for 12:15 P.M. Monday and Tuesday. Round Table Luncheons scheduled for Monday are:

1. "Moral Implications of Heart Transplants"
   Norman E. Shumway, M.D.
   Palo Alto, California
2. "Innovations in Regional Blocks of the Upper Extremity"
   Van S. Lawrence, M.D., Rochester
3. "Diagnostic Aids in the Evaluation of the Hemolytic Anemias"
   Harry Jacob, M.D.
   Boston, Mass.
4. "An Endoscopic New Look at Gastric Lesions"
   Jack A. Vennes, M.D.
   Minneapolis
5. "The Over-Achiever—Why He Fails"
   Harold R. Martin, M.D. and
   Wendell M. Swenson, Ph.D.
   Rochester
6. "Treatment and Consideration of Plantar Warts"
   Robert R. Kierland, M.D.
   Rochester
7. "Risks of Treatment—Medical and Legal"
   Mr. Curtis D. Forslund
   Minneapolis

Topics scheduled for discussion at the Tuesday Round Table Luncheons include:

1. "To Tell or Not to Tell"
   Rev. Dr. Paul B. McCleave
   Chicago
2. "General Anesthesia in the Traumatized Patient"
   Joseph J. Buckley, M.D.
   University of Minnesota
3. "Transplants—The Surgeon's Philosophy"
   John S. Najarian, M.D.
   University of Minnesota
4. "Family Practice"
   Richard V. Ebert, M.D.
   University of Minnesota
   Benjamin F. Fuller, M.D.
   University of Minnesota
5. "Learning Difficulties in Children"
   John S. Pearson, Clinical Psychologist
   Rochester
   Mrs. Jean S. Osman
   Rochester
6. "The Keogh Bill—Fact and Fancy"
   Mr. Jule M. Hannaford
   Minneapolis

Annual Banquet

Seventeen Minnesota physicians who have practiced medicine for 50 years will be honored at the Annual Banquet Tuesday, May 14, at 7:00 P.M. at the Kahler Hotel. The Annual Banquet will be preceded at 6:00 P.M. by the President's Reception.

The Southern Minnesota Medical Association will present its annual medal award at the banquet to the physician who has prepared the outstanding scientific exhibit. In addition, the 1968 recipient of the distinguished service award will be announced. Banquet guests are cordially invited to remain for an evening of outstanding entertainment, including a floor show and dancing. The price of the banquet ticket also includes a late evening buffet.

The annual Bridge Tournament will be held Monday, May 13, in the Holiday Inn.

Pre-Registration

Pre-register for the meeting in Rochester. By completing the registration card enclosed with the monthly Newspage and returning it to the State Office before May 5, physicians can be certain that their badge will be waiting for them at the advance registration desk in the Mayo Civic Auditorium.

SCIENTIFIC PROGRAM

Mayo Civic Auditorium

Monday, May 13, 1968

A.M.

HEART

John W. LaBree, Minneapolis—Chairman

9:00 **New Concepts in the Management of Patients with Acute Myocardial Infarction**
Edward A. Ryan, Duluth
Emilio R. Giuliani, Rochester
Harold T. Mankin, Rochester
Carlos E. Harrison, Jr., Rochester

10:30 Visit scientific and technical exhibits

11:15 **Heart Transplantation—Present Considerations**
Norman E. Shumway, Jr., Palo Alto, California

P.M.

12:15 **Round Table Luncheons**

1:30 Visit scientific and technical exhibits

2:00 **BLOOD**
Robert A. Green, Minneapolis—Chairman
ROTATING GROUP DISCUSSIONS ON DISORDERS OF THE BLOOD

Polycythemia Vera—Clinical Aspects and Treatment
Howard L. Horns, Minneapolis
Murray N. Silverstein, Rochester

Multiple Myeloma—Diagnosis and Current Status of Therapy
James L. McKenna, Minneapolis
James R. McArthur, Salt Lake City

Problems in Diagnosis and Management of Acute Leukemia
Joseph M. Kiely, Rochester
F. Bruce Lewis, Minneapolis

3:00 **Mechanisms of Hemolysis in Hemolytic Anemia**
Harry S. Jacob, Boston, Mass.

3:30 Visit scientific and technical exhibits

4:00 **Panel of Experts—Leukemia, Myeloma and Polycythemia**
Robert A. Green, Moderator
All group leaders participating including Doctors Jacob, Horns, Kiely, Lewis, McArthur, McKenna, and Silverstein

Tuesday, May 14, 1968

A.M.

9:00 **SHOCK**
Richard C. Lillehei, Minneapolis—Chairman

Pathogenesis and Management of Endotoxin Shock
Wesley W. Spink, Minneapolis

The Choice of Antibiotics in Management of Bacteremia and Shock
William J. Martin, Rochester

Monitoring of Patients in Shock
Richard C. Lillehei, Minneapolis

10:30 Visit scientific and technical exhibits

11:00 **Meet the Chiefs**
Introductions—*Robert B. Howard*
Dean of Medical Sciences
University of Minnesota
John S. Najarian
Professor and Head
Department of Surgery
Richard V. Ebert
Professor and Head
Department of Internal Medicine
John J. Sciarra
Professor and Head
Department of Obstetrics and Gynecology
Michael M. Paparella
Professor and Head
Department of Otolaryngology

P.M.

12:15 **Round Table Luncheons**

1:30 Visit scientific and technical exhibits

2:00 **BONES**
Harry B. Hall, Minneapolis—Chairman

Bone Decisions by the Decade
Edward L. Salovich, Minneapolis
Leonard O. Langer, Jr., Minneapolis

2:30 *Richard H. Jones, Minneapolis*
H. Wilson Godfrey, Minneapolis

3:15 Visit scientific and technical exhibits

4:00 **Bone Decisions by the Decade—(continued)**
Harry B. Hall, Minneapolis
S. Hartley Calin, Minneapolis

4:30 **Diagnosis and Treatment of Benign and Malignant Tumors of Bone**
John C. Ivins, Rochester
David C. Dahlin, Rochester
Harry F. Bisel, Rochester

Tuesday Evening

7:00 **Annual Banquet**
Reception at 6:00 p.m.
Presentations and Entertainment
Dancing and Late Evening Buffet

Wednesday Morning, May 15, 1968

A.M.

9:00 SEX

Maurice J. Martin, Rochester, and
Richard M. Steinhilber, Rochester—
Co-chairmen

Marital Sexual Problems
James P. Semmens
Oakland, California

10:00 Visit scientific and technical exhibits

10:30 **Panel on "Sexual Problems"**
M. J. Martin, Rochester—Moderator
James P. Semmens
Oakland, California
Werner E. Kaese
Rochester
Gerhard Neubeck, Ph.D.
Family Counselling Service
University of Minnesota

Round Table Luncheons

Monday, May 13, 1968

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Norman E. Shumway, M.D., Palo Alto, California

Innovations in Regional Blocks of the Upper Extremity
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Learning Difficulties in Children
John S. Pearson, Clinical Psychologist, Rochester
Mrs. Jean S. Osman, Rochester

The Keogh Bill—Fact and Fancy
Mr. Jule M. Hannaford, Minneapolis

Seeing Snakes

Perhaps the most lurid experience that I can remember in the transferring of patients is the time I had a delirium tremens case, with four policemen strategically placed so that the lithe wriggling patient could not escape through any of the apertures of the ambulance which had no doors to close the patient in. All the way to Bellevue I caught "snakes" with him. Poor devil, he saw them on the floor, the sides of the bus, under the blankets, everywhere, crawling and hissing at him. Many of the cases were quite prosaic: old people with chronic illnesses, tuberculosis patients, people recovering from fractures, vagrants, and the like. It was heavy, gruelling work at that time but I would not have had it otherwise, for this intimate daily and nightly contact with the old Bellevue brought me closer to the very heartbeat of my native city.*

*Emily Barringer, M.D.: Memoirs of A Lady Ambulance Surgeon, Bowery to Bellevue, 1950.

I would rather that the people should wonder why I wasn't President than why I am.—Salmon P. Chase

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He and I have been dead these two years, but we don't choose to have it known.
—Lord Chesterfield



NORTHLANDS REGIONAL MEDICAL PROGRAM

REGIONAL PROGRAM FOR HEART DISEASE, CANCER AND STROKE

The social revolution of our time now focuses on the delivery of health services. "Creative federalism" is not new. It has expanded steadily with the increasing demands of a progressively more advanced and more complicated society. Focuses on employment, agriculture, and rural electrification in the 1930's progressed onward through welfare, education, research and hospital construction. Current involvement in the delivery of medical care began with several fundamental pronouncements:

(1) Medical care is no longer either a personal privilege or a public charity. It is a fundamental human right of all citizens.

(2) Every patient should receive all of the benefits of the latest scientific knowledge.

(3) Each state, each region and each sub-regional area should develop a system of effective health planning.

The Regional Medical Program Act comprises a part of the social revolution in Medicine. In many ways this program simulates the federal agricultural program started over 35 years ago. Recognizing the eventual magnitude of change this program might create, Congress specified an initial phase of planning and development, to last from a few months to several years.

The Northlands Regional Medical Program planning grant was awarded January 1, 1967. We are now in the second year of this planning phase.

What has been accomplished in the fifteen months?

(1) The program organized an extensive involvement of medical centers, professional organizations, health agencies, and health care personnel on a cooperative basis.

(2) Working committees containing many capable and respected physicians, administrators, paramedical and lay personnel have spent literally hundreds of hours developing the program.

(3) A series of basic studies necessary for effective planning and implementation have been instigated. Those most completely developed are as follows:

(a) Development of a Minnesota Health Personnel Databook.

(b) A survey of continuing medical education of physicians.

(c) An evaluation of the TV series "Monday for Medicine."

(d) A plan for a state-wide program for intensive coronary care units.

(e) A rural health care study analyzing three component aspects.

(f) A study for postgraduate education in pediatric cardiology.

(g) A survey of existing and potential resources relating to the care of patients with stroke.

(h) A study to determine feasibility of collecting data and integrating care of pediatric solid tumor patients.

(i) A study of telephonic transmission of computer analysis of multi-channel electrocardiograms.

(j) A computer analysis of the care and results of coronary artery disease.

(k) A study of changing food habits and serum cholesterol levels in free living families.

The Northlands Regional Medical Program is a program developed by the people of Minnesota for the people of Minnesota. Principal medical centers and other organizations have become involved. We need to develop interest and participation in areas distant from the metropolitan center. We solicit your suggestions for appropriate projects in the various sub-regional areas of the state.

Winston R. Miller, M.D., F.A.C.P.
Program Director

John Hunter—Resurrectionist

For years he practically haunted the Irish giant, Byrne (born O'Brien) whose eight-foot skeleton he coveted. The poor man desperately tried to evade him, but every time Hunter managed to track him down. Byrne willed that when he died his body should be placed in a lead coffin, taken out to sea and sunk; at his death the body was placed under heavy guard. Hunter found out when the men on duty had gone off for a drink. He went to the tavern and bribed them with five hundred pounds which he had to borrow, and was able to arrange for the removal of the corpse in a hackney-coach. It was then transferred to his own carriage and taken to Earl's Court. He sectioned the body, removed the flesh by boiling in a huge vat, and reassembled the skeleton, which later hung in his study. In the portrait Joshua Reynolds painted of Hunter, the dangling legs of the giant can be seen in the background.*

*Sarah R. Riedman: Masters of the Scalpel, 1962.

Salutation to the Dawn*

Look to this day, for it is life. The very life of life.
In its brief course lie all the verities
And all the realities of your existence.
The bliss of growth. The glory of action. The splendor of beauty.
For yesterday is but a dream. And tomorrow is only a vision.
But this day well lived makes every yesterday a dream of happiness
And every tomorrow a vision of hope.
Look well, therefore, to this day.
Such is the salutation to the dawn.—Kalidasa

*Originally written in Sanskrit by Kalidasa, a Hindu poet and dramatist. Most literary historians agree that it was written in about the third century. Kalidasa was known as the Shakespeare of India. Contributed by Doctors Vernon D. E. Smith, Gerhard E. Knutson, and Neil M. Palm, St. Paul.



Physician's Diary

Bust rather than rust.—Forbes Epigrams

Dr. Robert W. Hollenhorst, Professor of Ophthalmology, Mayo Graduate School of Medicine, has been elected as a member of the Board of Examiners of the American Board of Ophthalmology.

* * *

NEW LOCATIONS: **Dr. Jack L. Strobel** has joined the Department of Pediatrics at the St. Louis Park Medical Center. . . . **Dr. John R. S. Remsberg,** specialist in internal medicine, has also joined the St. Louis Park Medical Center. . . . **Dr. George C. Bingham** has opened up new offices in Olivia. . . . **Dr. Robert Scanlan,** a Mayo Clinic specialist in diagnostic X-ray, has joined the staff of the Good Samaritan Hospital in Los Angeles. . . . **Dr. George W. Clifford** has retired from the practice of medicine in Alexandria. . . . **Dr. John Schotzko** has joined the Blue Earth Medical Center. . . . **Dr. Robert D. Mathison** has opened up a general medical practice in Plainview. . . . **Dr. K. L. Dedeker** has returned from military service and is again associated with the Martinson Clinic in Wayzata. . . . **Dr. Norman Hoover,** an orthopedic surgeon at the Mayo Clinic, has resigned to devote his energies fulltime to improving medicine in South Vietnam. . . . **Dr. Peter Foderick** intends to leave Hallock to do post graduate work at the University of Minnesota. . . . **Dr. Lee N. Podoll** has become associated with the Valley Medical Center in Spring Valley. . . . **Dr. Charles Ehlen** has joined the staff of the Mound Medical Clinic. . . . **Dr. Robert Sauer** is Preston's new physician. . . . **Dr. Rudolph Rosenquist** has joined the Glencoe Medical Clinic staff for a temporary period of time. **Dr. L. J. Hoyer** terminated his association of thirty years at the Windom Clinic April 1. . . . **Dr. Lloyd C. Gilman** will take a leave of absence for one year from the Lakeland Medical Center in Willmar to complete a residency in urology at Creighton University and the Omaha Veterans Hospital at Omaha. . . . **Dr. Richard Shepard** has joined the medical staff at the Albert Lea Medical and Surgical Center. . . . **Dr. John K. Meinert,** a member of the staff at the Lakeland Medical Center in Willmar, has volunteered to serve professionally on board the Hope, for a two-month period.

* * *

Doctors Raymond A. Allen, William F. Taylor, Mark S. Schwartz, Robert V. Pierre, Walter R. Lysak, Gordon L. Moore, II, Frank J. Leary, Leo J. Davis, Jr. and **Claude D. Arnaud** have been appointed to the staff of the Mayo Clinic in Rochester.

* * *

Dr. Daniel J. Moos, Wayzata, has been elected president of the Northwestern Hospital medical staff for 1968, and **Dr. John T. Kelly,** Robbinsdale, was re-elected president of the St. Mary's Hospital medical staff. **Dr. Berton Mitchell** was re-elected vice-president and **Dr. Milton Seifert, Jr.** was elected secretary-treasurer of St. Mary's.

* * *

Dr. James T. Priestley, senior surgeon of the Mayo Clinic, was inducted as an honorary fellow of the Royal College of Surgeons of England.

* * *

The Nicollet-LeSueur County Medical Society elected **Doctor A. D. Walden,** president, **Dr. B. P. Grimes,** vice president, and **Dr. G. F. Engstrom,** secretary-treasurer, for the year 1968.

* * *

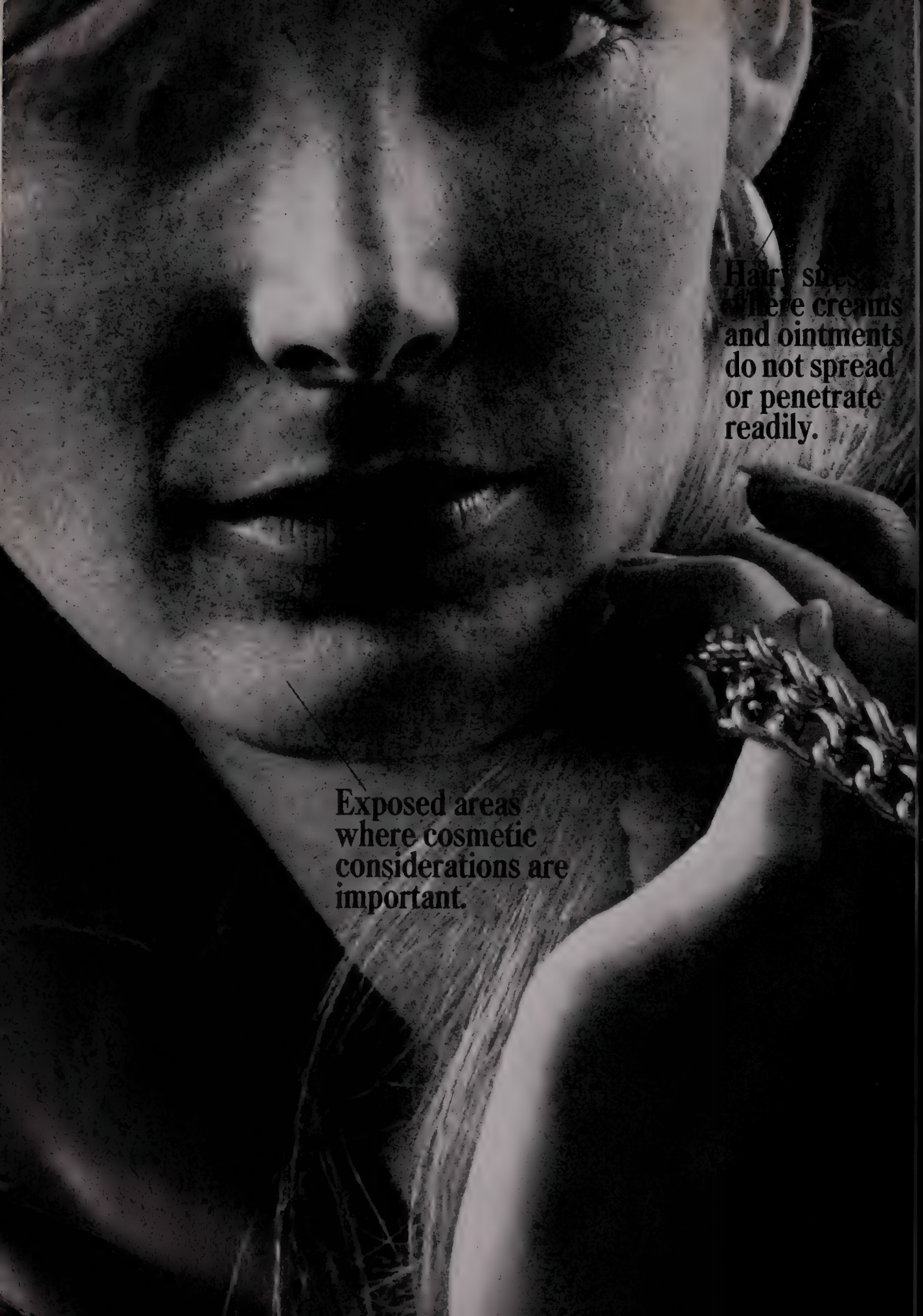
Dr. William A. Nolen, Litchfield, has been appointed to the consulting surgical staff at Hennepin County General Hospital, and **Dr. A. E. Magnuson** of Wheaton, was appointed county coroner by the county commissioners of that town.

* * *

Dr. Owen Wangensteen, Minneapolis, will receive the 1968 Distinguished Service Award of the American Medical Association at the AMA convention in San Francisco next June.

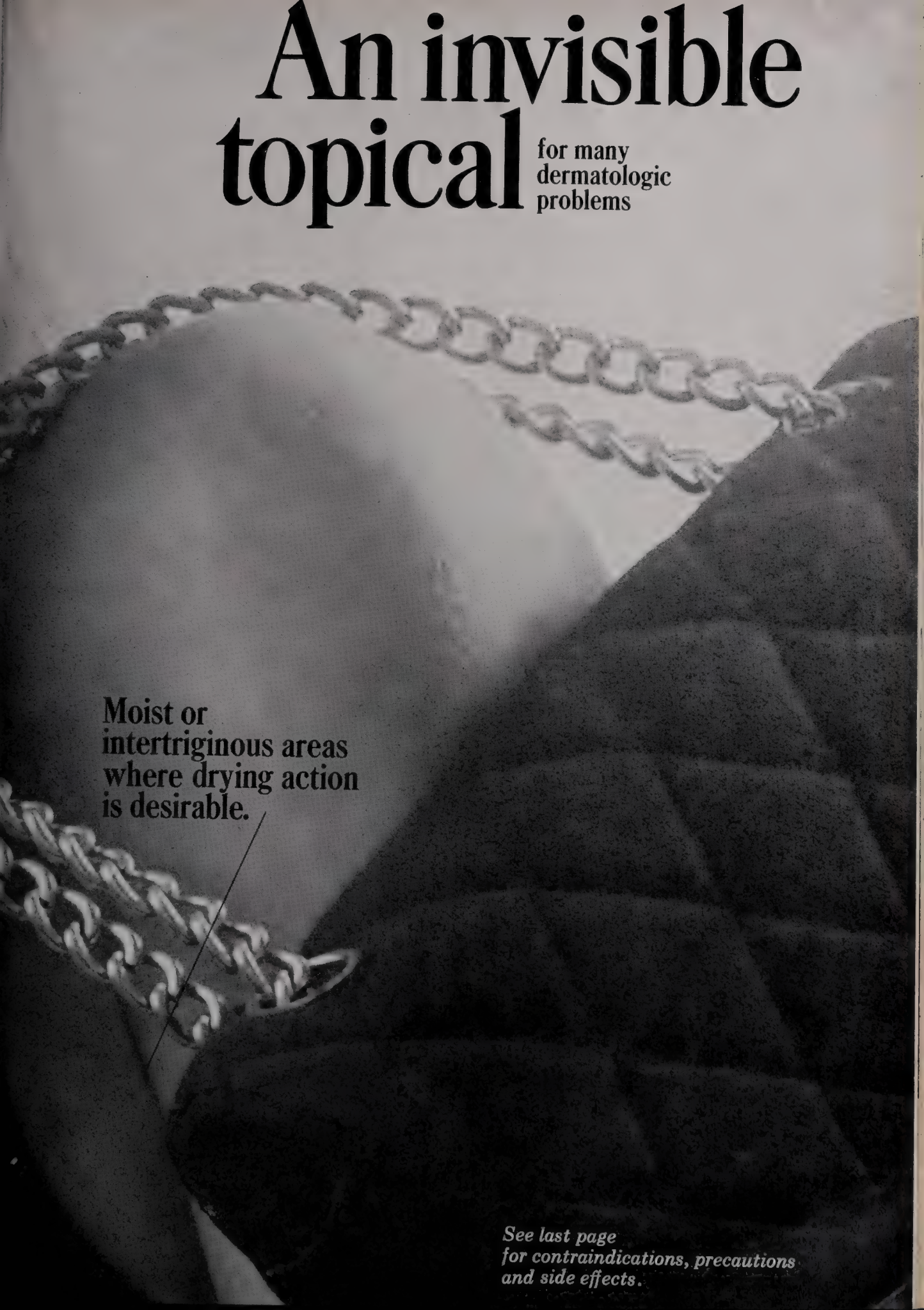
* * *

Dr. Michael D. Levitt, instructor at Boston University Medical Center, has been appointed assistant professor of medicine in the gastrointestinal unit of the department of medicine, University of Minnesota.


Hairy sites where creams and ointments do not spread or penetrate readily.
Exposed areas where cosmetic considerations are important.

An invisible topical

for many dermatologic problems



Moist or intertriginous areas where drying action is desirable.

See last page for contraindications, precautions and side effects.

Structurally unique topical steroid in propylene glycol vehicle produces rapid response in many dermatoses.

Synalar Solution produces rapid antiinflammatory, antipruritic action through its unique topical corticosteroid, fluocinolone acetonide. The propylene glycol vehicle provides additional benefits for therapy at problem sites where it is difficult to achieve contact between the lesion and medication – or where creams or ointments may make the lesions worse. Synalar Solution has proved particularly valuable in the symptomatic treatment of seborrheic dermatitis of the scalp, nasolabial folds, eyebrows, ears, and in flexural folds such as the axillae, inframammary, umbilical and anocrural areas. It has also been reported to achieve excellent results in the adjunctive management of atopic dermatitis, contact dermatitis, neurodermatitis, nummular eczema, psoriasis, and sweat retention syndromes in these problem sites.

Penetrates the hairy sites.

In many areas of the body, hair gets in the way of treating the underlying dermatitis. The propylene glycol vehicle of Synalar Solution permits penetration and dispersion at sites where creams and ointments do not readily penetrate. May be applied without matting of hair.

Ideal for moist or intertriginous areas.

Propylene glycol is strongly hygroscopic and is especially useful where sweat retention is a problem. Its low surface tension permits easy spreadability in difficult-to-treat body areas. A number of studies have also shown that propylene glycol has inherent antimicrobial activity.



Cosmetically acceptable for exposed areas.

The propylene glycol vehicle of Synalar Solution possesses many useful cosmetic properties. Clear and greaseless, it is not sticky or messy, will not stain clothing or skin.
In exposed areas of the body where cosmetic appeal is important, Synalar Solution shows nothing but results.

Economical—a little goes a long way.

Because of the properties of propylene glycol and the milligram potency of fluocinolone acetonide, a small quantity of Synalar Solution goes a long way. Also, the prescription price of a 20 cc. plastic squeeze bottle of Synalar Solution is surprisingly low. Thus, your patients obtain economy with the proved efficacy of a potent, truly advanced topical corticosteroid.

Contraindications: Tuberculous, fungal, and most viral lesions of the skin (including herpes simplex, vaccinia, and varicella). Not for ophthalmic use. Contraindicated in individuals with a history of hypersensitivity to any of the components.

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(Continued from page 747)

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Minnesota Medicine at a Glance

Bronchodilator Solution Postoperative—*Ratelle et al.* Page 605

Any procedure or medication that would be useful in speeding the recovery of a patient from anesthesia should also be worthwhile in aiding in a surgical recovery. The studies of Ratelle et al. indicate that the use of a bronchodilator solution was effective in this regard.

The Cytologic Evaluation of Early Pregnancy—*Adcock* Page 611

Vaginal smears taken during pregnancy in threatened and habitual abortion are of prognostic value and identify those pregnancies in which hormonal therapy may be indicated. Vaginal smears are readily obtained, relatively inexpensive, can be repeated frequently and are available with little delay.

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Hyponatremia—*Segar and Moore* Page 625

In recent years, an interesting syndrome, that of hyponatremia associated with excessive renal losses of sodium, has been linked with certain cases of bronchogenic carcinoma. Patients with this disorder fail to curtail thirst despite a diminished urinary volume, which results in an expanded extracellular water volume. In addition, renal sodium excretion is excessive, despite low serum sodium concentrations. A resume of investigations in the aspects of this phenomenon is presented.

Chondrosarcoma of the Sternum—*Larson et al.* Page 679

Tumors of the sternum, either benign or malignant, are fortunately rare. When encountered, however, they can be effectively managed by currently available surgical techniques. The authors present a case and also a description of the surgical procedure required to reconstruct chest wall continuity. En-bloc excision and chest wall reconstruction, tailored to meet the individual requirements of these specific patients, are the essentials of successful management of tumors of the sternum.

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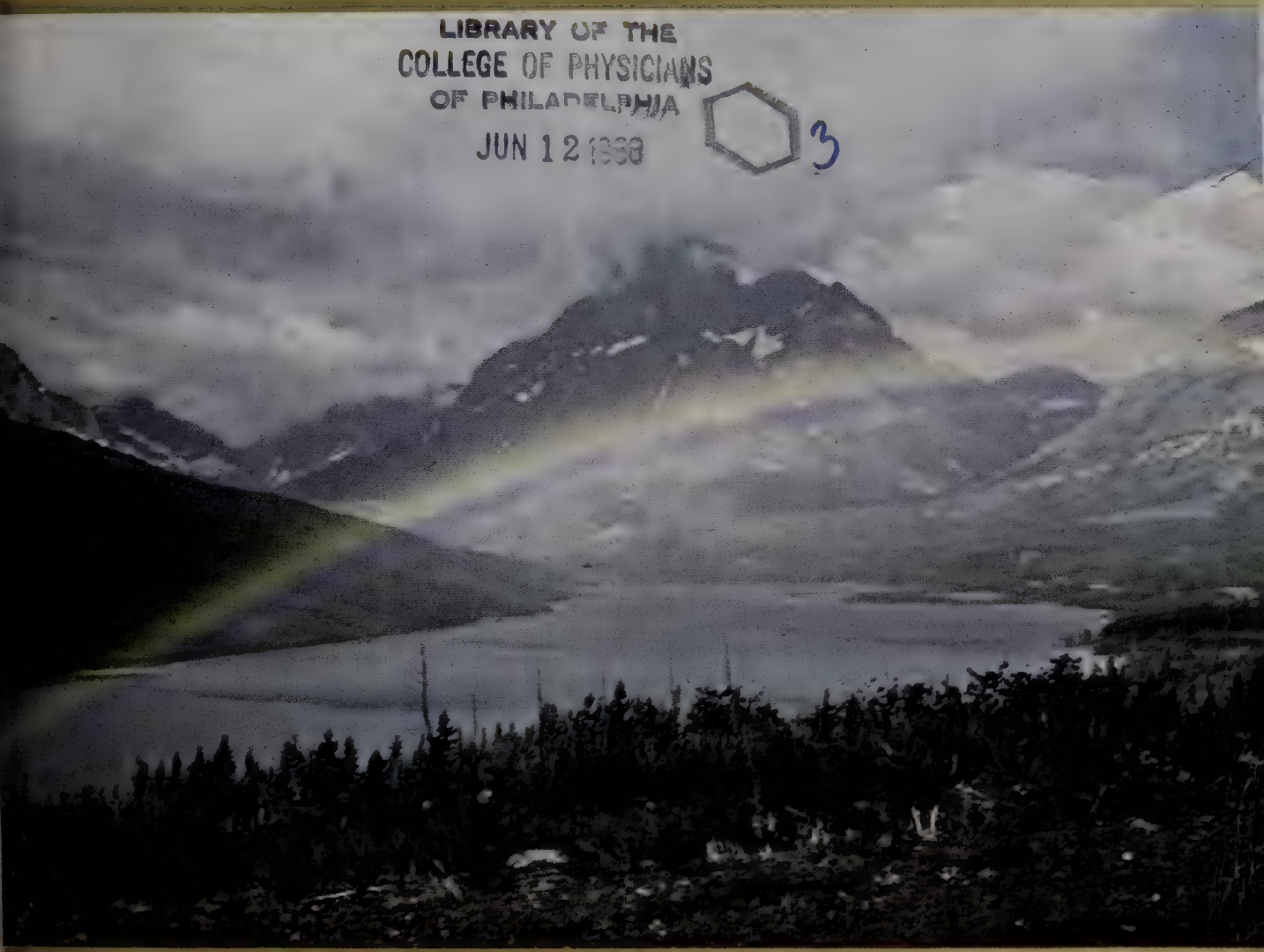
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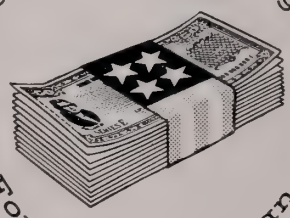
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Meet the President



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President's Letter

Academic Medicine

SINCE THE TURN of the century there has been a gradually increasing number of men turning to what is called Academic Medicine, and the tendency is to separate these men from those in the Practice of Medicine.

In this country men of such caliber as Halsted, Osler, Kelly and Welch were of the early group of full-time professors of Surgery, Medicine, Gynecology, and Pathology; and under their impetus others were trained specifically to become full-time teachers. Some of Halsted's men remained in training for seven to ten years and then went to occupy full-time teaching posts.

In the last twenty years, particularly under the influence of Doctor Wangensteen, the increase in the full-time Academic Surgeon has been fantastic; young men enter training with the idea that they will stay in Academic surroundings for the full course of their career, becoming highly trained, not only in the practice of surgery but also in research.

This increase of Academics has led to some misunderstanding with those in practice and vice versa, neither side fully comprehending the problems of the other.

In the 1920s many of the Chairs of Medicine and Surgery were held by part-time men, the Clinical Professors, whose main concern was the training of clinical men with little time for or knowledge of research. It is true that many fine surgeons have evolved under this system; however, as medicine and surgery developed rapidly the clinical professor became more frustrated. He was unable to keep up with, let alone get ahead of the tremendous growth of knowledge, and at the same time was unable to give proper attention to his ever increasing patient load. He found it difficult to be both fish and fowl, but had to choose between them.

There are many frustrations for the man who chooses an Academic career, such as some loss of independence, interdepartmental skirmishes, decline in income, administrative responsibilities, and less personal rapport with patients. However, he does have the advantages of more time for reading and research, ease of consultation, the protection of the institution, and the satisfaction of developing young men to become highly qualified practitioners or teachers of medicine or surgery in their own right.

The Practitioner also has many advantages, such as a larger income, greater independence, freedom of movement, a more personal relationship with his patients. However, his disadvantages consist of full responsibility for his patients and too little time to support and sustain a large patient load.

There has developed a third type of doctor:

Continued to page 800.

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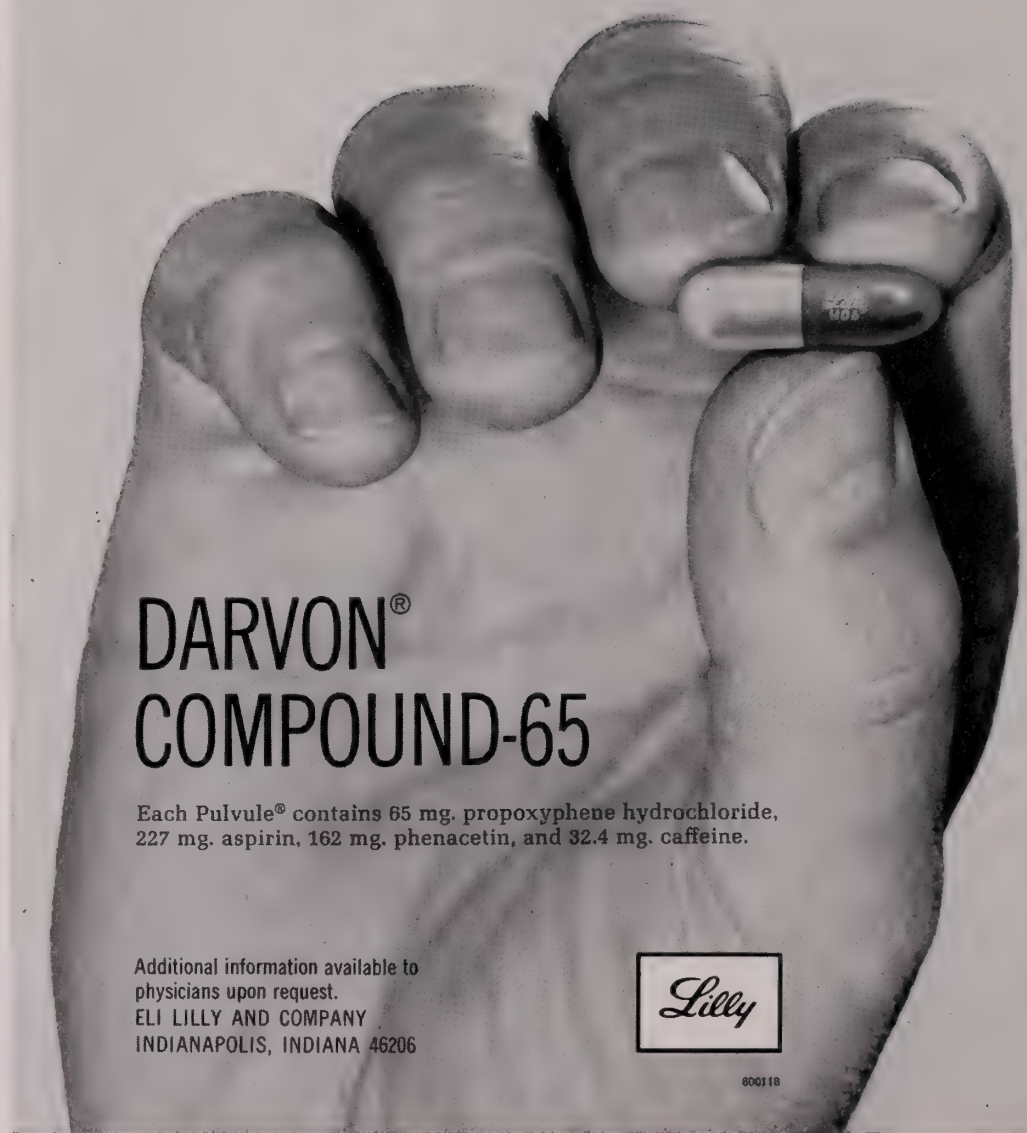
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The Evaluation and Treatment of Hydrocephalus

DONLIN M. LONG, M.D.*
SHELLEY N. CHOU, M.D.*
LYLE A. FRENCH, M.D.*
Minneapolis, Minnesota

THE SERIOUS PROGNOSIS of untreated hydrocephalus is now thoroughly documented and the need for prompt evaluation and surgical therapy is well accepted.[20] Laurence has reported upon the natural history of hydrocephalus and recorded a 46 per cent mortality in untreated cases. Of the survivors, only 18 per cent had I.Q.s greater than 85.[9,10] Foltz and Shurtleff reported even less optimistic statistics. Only 22 per cent of their patients survived for five years without surgical therapy, and of the untreated cases, only 5.5 per cent had I.Q.s of 75 or higher.[6]

Over the years a variety of operations have been devised for the control of hydrocephalus. Each has had its enthusiasts; but in general, salvage rates of less than 50 per cent have been reported. In 1952 Nulsen and Spitz introduced a unidirectional ventriculo-atrial shunt.[14] This technique of shunting excess spinal fluid from the cerebral ventricles to the vascular compartment has proved of great value and has become the standard method for the treatment of hydrocephalus. Many modifications of the original system are in use, but the basic principle remains the same.

The ventriculo-atrial shunt has now been in use long enough to permit assessment of its value for control of hydrocephalus and to allow comparisons with the results of other procedures. This review of 230 patients operated upon at the University of Minnesota Hospitals from January 1, 1938, to July 1, 1967, has been made to provide an accurate evaluation of the results of the various kinds of operative procedures undertaken in the treatment of hydrocephalus. Special emphasis has been placed upon the 93 patients treated since 1961 in whom some type of ventriculo-atrial shunt was employed as the primary therapy for hydrocephalus.

Methods

This investigation is based upon 230 patients

*Department of Surgery, Division of Neurosurgery, University of Minnesota Medical School.

with hydrocephalus, 87 of whom were treated between 1938 and 1951 and have been previously reviewed by Haines.[7] Between 1938 and 1960 a variety of operative procedures were utilized; from 1960 until the present time the ventriculo-atrial shunt has been employed primarily for the control of hydrocephalus.

The patients were all treated at the University of Minnesota Hospitals and were initially evaluated on either the Pediatric or the Neurosurgical Services. The standard evaluation consisted of complete historical and general physical examinations and complete neurological examinations. Head circumferences were obtained on a serial basis. Roentgenograms of the chest and skull, hemogram and urinalysis were also obtained.

The majority of the patients had subdural taps, communication studies and an air study of some type prior to operation.

Most of the patients with associated meningocele* or encephalocele underwent definitive repair prior to a shunt procedure; operative procedures for the correction of orthopedic, urologic and other defects were undertaken when indicated.

Nearly all operative procedures were performed under general anesthesia. The procedures themselves were standardized and followed the accepted techniques described in the literature (Table 2). After operation the patients were followed on a regular basis and evaluated in the Neurosurgical Clinic. Regular measurements of head size and estimates of functional capacity as well as neurological status were made. No formal psychometrics were obtained. The average follow-up in those cases with ventriculo-atrial shunts was 32 months, with the longest follow-up period being eight years.

The standard ventriculo-atrial shunt was the Pudenz-Heyer medium pressure valve. As soon as it became available, a flushing device was incorporated into this system and has been a part of the shunt procedure since 1961. A small number of Holter valves were utilized as well.

*See Test Your Word Score Page 797.

TABLE 1

Cause or Type of Hydrocephalus—1951 to Present

Communicating, cause?	32
Noncommunicating, cause?	19
Myelomeningocele	34
Encephalocele	10
Meningitis	14
Other congenital defect	17
Unknown or other	17
	143

TABLE 2

Operations for Hydrocephalus

	Number	Mortality
Choroid plexus coagulation	34	9.4%
Third ventriculostomy	21	33.0%
Lumbar-peritoneal	11	.....
Ventriculo-peritoneal	4	.....
Ventriculo-mastoid	20	14.3%
Other	13	15.0%
More than one	10	.....
Ventriculo-atrial	81	7.0%
Ventriculo-atrial + other	12	.....

Findings

Types of Hydrocephalus

The majority of the hydrocephalics were of the noncommunicating variety; the single most common cause of hydrocephalus was the Arnold-Chiari malformation associated with a myelomeningocele (Table 1).

Operative Procedures

In the 87 patients operated upon in the period from 1938 to 1951, 119 operations were performed (Table 2). In the original evaluation by Haines, 35.2 per cent of these patients were found to have adequate control of hydrocephalus and 43.2 per cent were found to have normal mentality.[7] Only a small percentage of these patients were available for long-term follow-up, but 10 were judged to have been normal for periods ranging from six to 19 years.

Mortality

It is interesting to note that third ventriculostomy and exploration of the posterior fossa with lysis of adhesions were associated with a 33 per cent mortality rate, which is consistent with the mortality published in other series (Table 2). Choroid plexus coagulation had only a 9.4 per cent mortality; but its control of hydrocephalus was felt to be adequate in only 37.5 per cent of cases. While quite effective in tumor cases in which a 65.7 per cent control of increase in intracranial pressure was obtained, the Torkildsen procedure, a shunting of fluid

from the ventricular system to the cisterna magna, was effective in only 18.2 per cent of nontumor cases of hydrocephalus.

In the 81 cases of ventriculo-atrial shunts which were not unusually complicated or did not also have choroid plexus coagulation, 118 operations were performed, an average of 1.5 operations per patient. In the nine cases which were considered unusually complicated, 59 operations were performed, a total of 6.6 per patient. Of these, 25 were ventriculo-atrial shunts: an average of 2.8 ventriculo-atrial shunts per patient. In the cases which had choroid plexus coagulation in addition to the ventriculo-atrial shunt, 16 operations were performed, an average of 5.3 operations per patient; five of these were ventriculo-atrial shunts or 1.5 shunts per patient.

Results of Operation

Results in this group are somewhat difficult to evaluate in the absence of formal psychometric and intelligence testing and because of the young age of many of these patients. For this reason, rather large groups have been used for classification purposes (Table 3). The patients were said to be functional mentally if they were competing with their peers in school or in other intellectual endeavors, or if it was the impression of parents and examining staff physicians that they were at a competitive level. If they were able to compete but were thought to be significantly less adequate than their peers, they were judged to be slightly retarded. It is probable that there is overlap between these two groups. Those who were noncompetitive were classified as seriously retarded.

Fifty-one per cent of these patients were considered to be functioning normally; an additional 16 per cent were thought to be slightly retarded. Combining these two groups provides a figure of 67 per cent who were functional from an intellectual standpoint. This evaluation does not include other neurological deficits. Twenty per cent of the patients were judged to be very retarded and 6 per cent had died. Most of these deaths occurred in patients with myelomeningoceles and were secondary to chronic urinary problems. The operative mortality was 7 per cent, a figure which will be explored in more detail in another part of this report.

TABLE 3
Results of Operation

	functional	severely retarded	dead
Ventriculo-atrial Ventriculo-atrial + Other	67%	20%	6%
All other operations			
1938-1951	35.2%	....	....
1951-1960	32%	33%	7%

In those patients undergoing operations other than ventriculo-atrial shunts, there were 96 operations in 46 patients, an average of 2.1 per patient. Twelve of these patients were judged to be normal and three to be slightly retarded, giving an overall competitive rate of 32.7 per cent. Fifteen patients were felt to be seriously retarded. Three expired due to nonoperative causes. The operative mortality in this group was 15 per cent (seven patients) and the follow-up was thought to be inadequate to make an evaluation in six patients.

Complications

Infection

The overall infection rate including both major and minor infections was 14 per cent. The infection rate in otherwise uncomplicated patients was 8.5 per cent; while in those patients considered unusually complicated, undergoing multiple operative procedures, the infection rate was 31 per cent. It must be emphasized that this infection rate does not represent primary infections. No attempt has been made to separate those cases which were complicated upon arrival at the University of Minnesota Hospitals or which had suffered previous infections or complications in other operative procedures performed prior to admission. Of the 10 operative infections occurring in the 81 otherwise uncomplicated cases, six followed postoperative cerebrospinal fluid fistulae secondary to inadequate shunt function. Thus in those cases without previous infection with adequately functioning ventriculo-atrial shunts postoperatively, the overall infection rate was only 4.9 per cent.

In addition to infections definitely related to the operative procedure, there were additional cases[11,19] in which the valve became infected during an episode of supposed septicemia secondary to urinary tract infection, pneumonia

or other upper respiratory infections.

Obstruction of the Catheter

Obstructions of the ventricular end of the catheter are usually secondary to envelopment by the choroid plexus or obstruction of the catheter lumen with detritus. This occurred 23 times in this series of cases. Obstruction of the atrial end of the catheter is usually secondary to thrombosis in the superior vena cava and is frequently the result of growth of the patient with gradual elevation of the atrial catheter into the superior vena cava or jugular vein. This occurred 18 times in this series. There were no cases of serious thromboembolic phenomena from venous or cardiac thrombosis. There were three instances in which an atrial catheter became disrupted and a portion of the catheter embolized to the right heart.[11] There were 12 cases in which some portion of the equipment was felt to be structurally incompetent, resulting in disruption of the shunting system. In three instances the valves inserted developed a malfunction and had to be replaced.

End Results

The overall results may then be summarized as follows: of 93 patients in whom some form of ventriculo-atrial shunting was employed as the primary treatment of hydrocephalus, 67 per cent were found to be competitive, 20 per cent were found to be very retarded, 6 per cent succumbed in the course of their illness due to nonoperative causes, and the operative mortality was 7 per cent. In two series of patients from this Clinic who were treated with operations other than the ventriculo-atrial shunt, the success rate varied from 33 to 42 per cent. The operative mortalities were 15 and 33 per cent in the two series.

Discussion

This entity appears to have been known since ancient times[7,18] and was clearly described by Vesalius in the sixteenth century. However, even after the classic papers of Key and Retzius demonstrating the circulation of the cerebrospinal fluid, the pathophysiological condition underlying hydrocephalus was thought by most authors to be meningeal hydrops.[7] It remained for Dandy and Blackfan to provide conclusive evidence that obstruction of the circulation or absorption of cerebrospinal fluid was responsible for hydrocephalus.[2] The process of cerebrospinal fluid production by the choroid plexus and circulation through the ventricles into the lumbar and cranial subarachnoid spaces with the eventual absorption in the cranial arachnoid villi was formulated in its modern form by Weed in 1917 and has been modified only slightly since that time.[21,22]

Shunt to Basal Cisterns

Shortly after Dandy's experimental work on this subject, several operations for the control of hydrocephalus were devised. Of these third ventriculostomy and choroid plexus coagulation have been most utilized. Third ventriculostomy consists of puncture of the lamina terminalis above the optic chiasm and/or puncture of the floor of the third ventricle as well, thus allowing the fluid contained within the obstructed ventricular system to escape into the basal cisterns and so circulate throughout the subarachnoid spaces.[3,4,5] Unilateral or bilateral endoscopic coagulation of the choroid plexus of the lateral ventricle was also used extensively before the introduction of the ventriculo-atrial shunt.[16] But the favorable results of choroid plexus coagulation and third ventriculostomy[18] have not been substantiated by other series, including our own. Lumbar-ureteral and ventriculo-ureteral shunts have proved successful in selected cases;[7] however, the number of candidates for the procedure in any group of hydrocephalics is not large and these operations have not been employed in our patients.

Shunt to Nonvascular Compartments

Attempts have been made to shunt spinal fluid to a variety of spaces besides the vascular compartment. Shunts into the subcutaneous tissue and into the marrow space have not proved successful.[7] In communicating hydrocephalus lumbar-subarachnoid to peritoneal cavity, shunts have proven effective in some instances; however, in our hands the shunts from ventricle to peritoneal cavity have not been successful for more than a few months because of loculation of fluid with adhesions and failure of absorption by the peritoneum. A few individuals have reported more success with this method. Ventriculo-pleural shunts have also been employed, but formation of adhesions from pleura to lung and failure of absorption

in this space have occurred with considerable frequency.[8] We now do not routinely employ these shunts in the primary treatment of hydrocephalus, though they may be of value in selected cases complicated by infection or as a temporizing measure when a vascular shunt is contraindicated for some reason. Ventriculomastoid shunts have been created but have commonly resulted in infection.[13] We have successfully used a ventriculo-sagittal sinus shunt in several adults with malignant brain tumors but have not employed this technique in children. Recently, a direct ventriculo-atrial shunt has been described, which requires thoracotomy and placement of the atrial catheter by cardiotomy; but it remains to be seen whether improved results will justify the use of an operation of this magnitude.

The Shunt Tubing

Early attempts at creating ventriculo-vascular shunts were confounded by the lack of an adequate shunt-tubing material. Finally in 1952 Nulson and Spitz introduced the Holter valve which consisted of unvalved ventricular and atrial catheters connected by a ball valve pumping device.[14] The standard method for the insertion of this shunt was described at that time. The ventricular catheter is placed preferably in the frontal horn of the lateral ventricle through a small parietal burr hole and connected to a subcutaneously placed pumping device over the mastoid region. The atrial catheter is placed in the right jugular vein, threaded down to the level of the mid-right atrium, and connected subcutaneously to the pumping device. In 1957 Pudenz and Sheldon introduced the Heyer valve which consisted of a straight ventricular catheter attached to a vascular catheter with a slit valve located at the intra-atrial end.[15] Again, this shunt was from right lateral ventricle subcutaneously into the right jugular vein and then into the heart. Later a flushing device or pump was included in the Pudenz system so that the function of the shunting system could be checked. Many modifications of these basic types have now been made and several systems are now available, but the method of insertion and the functional principles remain the same.

Evaluation of Suspected Hydrocephalus

As a result of our experience to date, we have now come to utilize a more or less standard evaluation procedure for the suspected hydrocephalic. In addition to routine historical and physical examination, a complete neurological examination and skull films are obtained. Bilateral subdural taps are performed to exclude the possibility of subdural hematoma. Following the subdural taps, 1 cc. of dilute Evan's Blue is injected into the right lateral ventricle. Fluid is then removed from the left lateral ventricle to be sure there is circulation from right to left. A lumbar puncture is performed and small amounts of fluid serially removed to determine if communication from ventricle to lumbar-subarachnoid space occurs. If no communication is present in 15 minutes the case is judged to be functionally noncommunicating. Recently we have been utilizing the intrathecal administration of a radioactive technetium-albumin complex and following the migration of this protein complex by serial scintillation scans, which provides a much more dynamic analysis of circulation of the spinal fluid. Following the communication study a limited ventriculogram is performed and, if it seems indicated, lumbar pneumoencephalography may also be utilized. In a few cases positive contrast ventriculography is necessary to delineate the process. As soon as the air is absorbed, a right ventriculo-atrial shunt is performed. It is now our practice to insert the ventricular catheter through a parietal burr hole and to place the tip at about the level of the coronal suture in order to avoid the choroid plexus. The pump or flushing device is placed behind the right ear in the burr hole, and the atrial catheter introduced into the jugular vein through a branch of the common facial vein with the tip of the atrial catheter placed in the mid-right atrium. We prefer to place this atrial catheter under x-ray control, though other methods using electrocardiogram and pressure wave changes have been described. Postoperatively there is no need to pump the shunting system, for it will function spontaneously, being constructed to flow at a specific pressure and to remain closed at all lower pressures.

Postoperative Evaluation

Patients are followed subsequently at regular intervals in the outpatient clinic. These

visits include measurement of head size and check of valve function. It is most important to be assured that the valve is functioning, and it is also important to follow the head growth curve. If the shunting procedure has been successful the head growth should cease until the head circumference has returned to the normal range for the patient's age and size. Head growth may then continue, but at the normal rate. If the head circumference remains outside the normal range and slow head growth continues, it may mean that the shunting system is inadequate. We also consider it most important for these children to receive prophylactic antibiotics if they have intercurrent infections. The urinary tract infections to which the myelomeningocele paraplegics are prone must be treated promptly. It is our usual practice to administer antibiotics to shunt patients in the course of viral or upper respiratory diseases as well.

Choice of Operative Procedure

As a result of this study we believe several statements can be made concerning the treatment of hydrocephalus. It seems unequivocal that the successful use of the ventriculo-atrial shunt will provide a higher percentage of functional individuals than the other methods for the treatment of hydrocephalus currently available. It also seems definite that the results of surgical treatment in hydrocephalus are significantly better than hopeful waiting. In our hands third ventriculostomy, choroid plexus coagulation, ventriculopleural, ventricular and/or subarachnoid-peritoneal shunts have not proven as effective as the vascular shunts. This does not mean, however, that these methods cannot be employed to advantage in many instances; indeed, they remain helpful adjuncts in the care of these patients. The mortality and morbidity of the vascular shunting operations are real but not great. Since the institution of these procedures, the infection rate has steadily decreased and the mortality rate is now less than 5 per cent.

References may be secured from the author or the reprints.

Assessment of Functional Recovery

Because of the young age of many of these children and since we do not have formal psychometric evaluations of all of them, it is impossible to completely characterize their functional state. Even accurate measurement of the I.Q. is not always possible in these cases, for it has been shown that there is a marked disparity between verbal and performance intelligence quotients in many of these children.[6] Nevertheless, we feel the judgment of the responsible physician and the parents can be sufficient for the purposes of this communication. How competitive these children will actually be must await reevaluation after a more significant number of them have advanced through school. Nor does this evaluation take into consideration the physical deficits which many of these children suffer. Foltz has indicated that the prognosis for hydrocephalics without significant neurological loss is much better than for those with associated myelomeningocele or other deficits, even when the latter are mentally intact.[6]

What the eventual salvage rate in hydrocephalus may be is still unknown. It is obvious that the ventriculo-atrial shunt is not a panacea for this disease but appears to be definitely superior to no treatment at all and is the most valuable of the multiple procedures in current use.

Summary

(1) A total of 230 patients with hydrocephalus were treated surgically at the University of Minnesota Hospitals from 1938 through 1967. (2) Eighty-one were treated with ventriculo-atrial shunts; 67 per cent of this group are functional individuals. (3) Twelve additional cases were treated with ventriculo-atrial shunts but also underwent multiple shunting procedures and were considered unusually complicated. (4) Twenty-one other combinations of procedures were utilized primarily before 1960. Of these patients only 37 per cent could be considered functional. (5) We have described our current plan for the evaluation and treatment of hydrocephalus.

I do not greatly care whether I have been right or wrong on any point, but I care a good deal about knowing which of the two I have been.—Samuel Butler

Periarteritis Nodosa

Complicated with Bilateral Spontaneous Massive Perirenal Hemorrhage

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PERIARTERITIS NODOSA is a systemic disease that involves the small and medium-sized arteries. It is characterized by an inflammatory reaction that results in necrosis and weakening of the vessel with secondary nodular thickening and fibrosis of the vessel wall, thrombosis, infarction, aneurysmal formation, and hemorrhage. Acute, subacute, and chronic phases may be seen simultaneously in the same organ. The etiology is unknown. However, some work by Rich[1] and by Rich and Gregory[2] lends support to the possibility that the disease might be due to a hypersensitivity reaction. Although the vascular lesions can occur in almost any organ, they reportedly are most commonly found in the kidneys (in about 80% of cases). The incidence of perirenal hematoma due to this disease is rather low, the first case reported with this complication being that of Schmidt[3] in 1908. Up until 1966 we were able to tabulate approximately 30 such cases,[4-12] to which we would like to add another. Bilateral perirenal hematoma due to this disease is rare. Up to 1966 we were able to find reports of four cases,[4,6,8,9] ours making a total of five.

Successful recognition of the microaneurysms within the kidneys by means of selective renal angiography prior to rupture of an aneurysm has been demonstrated by Ostrum and Soder[11] and by Horner and associates.[12]

Report of Case

A 48-year-old male farm worker was admitted to the Mayo Clinic and hospitalized on September 25, 1962, with the complaint of progressive left ear deafness for five months. Eight weeks before admission he had noticed decreased auditory acuity in the right ear associated with the onset of episcleritis in the right eye; this spread to involve the left eye approximately one month before admission. At this time he also noted the onset of a left frontoparietal throbbing pain, worse at night, unassociated with rhinorrhea, lacrimation, or scotomata, and usually relieved by ergotamine with caffeine (Cafergot), belladonna alkaloids, and acetophenetidin (Wigraine), or large doses of salicylates. During the six weeks before

*Mayo Clinic and Mayo Foundation: Section of Medicine.
**Mayo Clinic and Mayo Foundation: Section of Urology.
†Mayo Clinic and Mayo Foundation: Section of Surgical Pathology.

admission his weight had dropped from 190 to 160 pounds, and for two weeks before admission he had had intense anorexia, nausea, and occasional vomiting, unrelated to the presence of headaches.

Physical Examination

On physical examination he weighed 160 pounds and had a temperature of 99.2 F, a pulse rate of 75/min, which was regular, and a blood pressure of 128/86 mm Hg. Examination revealed a nerve-type hearing loss. Bilateral episcleritis was present without impaired vision; the optic fundi were normal. The edge of the liver was palpable on inspiration but did not seem enlarged. Moderate pain with tenderness was present over the left temporomandibular joint and over the right heel. The left gastrocnemius muscle was tender to pressure.

Urinalysis, determination of blood hemoglobin and urea, complete serologic examination, and roentgenographic examination of the chest, temporomandibular joints, esophagus, stomach, colon, small intestine, and head did not show any abnormality. A diverticulum was noted in the third portion of the duodenum. The leukocyte count was 9,100/cu mm of blood, with 91% neutrophils. The sedimentation rate was 30 mm in one hour (Westergren method). The flocculation test for rheumatoid factor was weakly reactive and a lupus erythematosus clot test was negative. The value for fasting blood sugar was 93 mg/100 ml. The sulfobromophthalein test for hepatic function showed a retention of 30% at the end of one hour. The bilirubin concentration was 0.5 mg/100 ml of serum direct and 0.7 mg indirect (van den Bergh reaction). The alkaline phosphatase value was 15 units/liter and the serum glutamic-oxalacetic transaminase activity was 0.93 μmole/hr/ml (normal values). Urinary amylase values were normal. Serum protein electrophoresis revealed the following values (gm/100 ml): albumin 3.05, α_1-globulin 0.58, α_2-globulin 0.87, β-globulin 1.02, γ-globulin 2.11, and total protein 7.63.

Hospitalization

During hospitalization the patient had a low-grade fever, his temperature increasing at times to 101 F. His headaches responded partially to the use of vasoconstricting drugs. The episcleritis responded poorly to the topical administration of steroids. Anorexia persisted. After several days, the sulfobromophthalein test showed 40% retention at the end of one hour; thymol turbidity was 3 units, cephalin-cholesterol flocculation negative, alkaline phosphatase 22.8/liter, sedimentation rate 50 mm in one hour, and the Quick prothrombin time 20 seconds. Repeated attempts at transthoracic needle biopsy of the liver revealed striated muscle, fat, and a very tiny fragment of liver tissue not adequate in amount for diagnosis. Repeat needle biopsy of the liver was advised but the patient refused. He was dismissed, being advised to rest at home for six weeks and then to return for further study.

Five days later the patient returned complaining of dull epigastric and right-upper-quadrant aching. Examination disclosed moderate rigidity in the right upper quadrant associated with tenderness. He had grade 3 albuminuria, grade 2 microhematuria, and grade 3 pyuria. The blood leukocyte count was 8,700 with 87% neutrophils. The sedimentation rate was 94 mm in one hour.

Two days after the second admission the patient was awakened from sleep by extremely severe right lower abdominal pain which was referred to the right groin and scrotum and to the right costovertebral angle. Acute right-lower-quadrant tenderness with the rebound phenomenon was present; the right side of the abdomen was rigid and there was marked tenderness to percussion in the right flank. At this time the hemoglobin value was 11.3 gm, the erythrocyte count 4,000,000/cu mm, and the leukocyte count 12,900 with 87% neutrophils. The sedimentation rate was 107 mm in one hour and the blood urea value 54 mg. An excretory urogram suggested the presence of a right renal mass, and subsequently a right retrograde pyelogram demonstrated a collecting system which seemed to be compressed but otherwise normal. Both renal outlines were poorly defined, but comparison of films revealed a definite increase in size of the right renal mass over a span of 72 hours. Further investigation of the indeterminate mass lesion by nephrotomagraphy versus exploratory laparotomy was considered.

Two days later the patient had a sudden recurrence of severe right midabdominal pain with shock and a drop in systolic blood pressure to 50 mm Hg. Exquisite tenderness in the right flank and right midabdomen was noted over a firm, ill-defined mass. The hemoglobin value was 10.4 gm.

An emergency operation on October 21, 1967, disclosed a moderate amount of free serous fluid in the peritoneal cavity. There was considerable edema in the right side of the abdomen, and a hematoma was present in the mesocolon. The gallbladder, stomach, duodenum, liver, pancreas, appendix, and colon were normal. The hematoma occupied most of the right renal region, extending down almost to the pelvic brim and medially as far as the great vessels. Several firm, palpable, subcapsular nodules were felt in the spleen but were not accessible to vision. In nearly the whole length of small bowel there were tiny, firm, discrete subserosal nodules which appeared to be within the lymphatics. One of these was biopsied but not identified by the pathologist. It was necessary to remove the kidney, adrenal, and 15 cm of the right ureter. Pathologic examination of the tissue revealed extensive perirenal hematoma formation, secondary to renal panarteritis with a cortical aneurysm 3 cm in diameter which had ruptured through the renal capsule. The ureter showed periureteral hemorrhage.

Subsequently the patient was given blood transfusions, steroids, and general supportive measures. However, eight days postoperatively he was seized with severe pain in the left flank associated with marked tenseness and tenderness of the left flank and left side of the abdomen. At this time the hemoglobin value dropped to 7.2 gm. It was felt that he had experienced another massive perirenal hemorrhage. Accordingly, the next day the left renal region was exposed and a large hematoma measuring 10 by 15 by 20 cm was identified as probably arising from the kidney inasmuch as the blood was concentrated immediately adjacent to the kidney, especially posteriorly. The capsule had been separated from the kidney over most of the posterior and lateral aspects by the hematoma. In the lateral margin of the lower pole of the kidney

was a defect 2 cm long and 0.5 cm wide filled with organized clot. It was assumed that bleeding with hematoma had resulted from an aneurysm secondary to periarteritis nodosa of the kidney. Renal biopsy for confirmation was considered extremely hazardous and therefore inadvisable. Large mattress sutures were placed and tied firmly over absorbable gelatin sponge (Gelfoam) to discourage further hemorrhage from the defect in the kidney. Convalescence was slow. The patient was dismissed one month postoperatively with instructions to continue on steroid therapy (methylprednisolone [Medrol], 10 mg four times a day).

On November 28, 1962, 11 days after discharge from the hospital, he was readmitted complaining of unusual dyspnea, orthopnea, ankle edema, and a cough productive of pinkish sputum. Roentgenograms of the chest showed a patchy infiltrate extending into the perihilar regions of both lungs, consistent with patchy interstitial hemorrhage. Temporary response to therapeutic measures was followed by gradual increase in cough and dyspnea. There was also recurrence of severe pain in the left lower abdominal quadrant and left flank. Three days later, clinical shock suddenly supervened and the patient died. The clinician felt that death was due to hypokalemia, uremia, and congestive failure.

Autopsy disclosed numerous vascular lesions in the liver and kidney and some in the gallbladder wall typical of panarteritis nodosa (periarteritis nodosa). The testes and adrenals showed hemorrhagic areas but no definite arterial lesions. The myocardium showed some scarring but no definite lesions. Multiple lesions of periarteritis were seen in the kidney.

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A Vinegar Cure

On one occasion a man came to Ibn Butlan* in his surgery at Aleppo complaining of hoarseness and complete loss of voice, and stating in reply to enquiries as to his occupation that he was a sifter of earth. Ibn Butlan made him drink half a pint of strong vinegar, whereupon he was seized with vomiting and threw up a quantity of mud with the vinegar, after which his throat was cleared and his speech became normal. Ibn Butlan said to his son and his pupils who were present, "Treat no one with this remedy or you will kill him. As for this man, some of the dust from the sieve had stuck in his gullet and nothing but vinegar could have dislodged it."**

*Ibn Butlan was a notable Arab Christian physician of the second century, A.D.
**Edward Browne: Arabian Medicine.

New Theory

First a new theory is attacked as absurd; then it is admitted to be true, but obvious and insignificant; finally it is seen to be so important that its adversaries claim that they themselves discovered it.—William James

It's the Law

The courts have established that, in a hospital, the physician's order on the patient's chart is a prescription order to dispense by nurse and to administer. In a nursing home, however, the chart order is merely an order to administer; not to dispense. Accordingly, unless the physician writes and signs a separate prescription order or personally transmits the order via telephone, the pharmacist must contact the physician for verification of the chart order. It should also be remembered that the physician's office nurse, as an agent of the physician, can legally transmit such information. The nursing home nurse, on the other hand, is an agent of the nursing home, not the physician, and cannot legally transmit the physician's order to dispense. Hence, the pharmacist's return call to the physician for verification.

The matter of prescription renewal (refill) authorization is one of continuing interprofessional concern. If the physician would indicate, whenever possible, the number of renewals or length of time for renewal authorization, considerable time could be saved by all parties and better patient care would result.

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Minnesota State Pharmaceutical Association

Waardenburg's Syndrome

This syndrome includes developmental anomalies of the eyelids, eyebrows, or nose root, pigmentary anomalies of the iris and head hair, and congenital deafness. Waardenburg in 1951 described the syndrome as a distinct entity. He found the anomalies in 12 of 840 deaf mutes. A regular dominant inheritance is the rule. Both sexes transmit these characteristics; in particular, there is father-to-son transmission.

Although the most serious defect in this syndrome is congenital deafness, it is seldom accepted and mentioned by patients. Dystopia canthorum is the most conspicuous feature. This displaced palpebral angle is readily apparent, especially in childhood. Other frequently observed anomalies consist of (1) lateral displacement of the medial canthi and lacrimal points; (2) a hyperplastic, broad, high nasal root; (3) hyperplasia of the medial portions of the eyebrows; (4) partial or total heterochromia iridum; and (5) partial, unilateral circumscribed albinism of the frontal head hair (white forelock). There may be blepharophimosis rather than ptosis, hypoplasia of the carunale and of the plica semilunaris, displacement of the puncta, especially the lower, laterally toward the cornea, and widened interpupillary distance. Occasionally other anomalies may be present, such as limitation of ocular movements, underdevelopment of the orbit, thickening of the tarsus, epicanthus, and such generalized defects as brachycephaly.

Waardenburg expressed the opinion that many of these abnormalities represent a persistence of the normal relationships in the embryo at eight to 10 weeks, so that the syndrome is parallel in nature to the persistence of the embryonic choroidal cleft.

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Liver

Liver: a large red organ thoughtfully provided by nature to be bilious with.
—Ambrose Bierce

Intravenous Regional Anesthesia*

A New Technique

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EVER SINCE Bier in 1908[8] and Holmes[9] in 1963 described in the literature the technique for intravenous regional anesthesia, it has been catching on like wildfire in most of the major clinics of this country and Europe. The technique is one that finds its greatest use in the general practice of medicine and surgery rather than in anesthesiology. It is with this thought in mind that I have presented this paper for a group not doing anesthesia full time. The technique is extremely simple and if carried out meticulously, the results approach 100% success.

Technique

Step No. 1.

A needle is carefully placed and anchored in a vein usually as close as possible to the site of surgery, or in the case of fracture, to the site of the injury. I prefer to use a No. 19 gauge Butterfly type needle, but any needle that is likely to stay in place easily will do. It is best to have a short extension of intravenous tubing from the needle to the syringe as this will facilitate wrapping of the arm in a later step.

Step No. 2

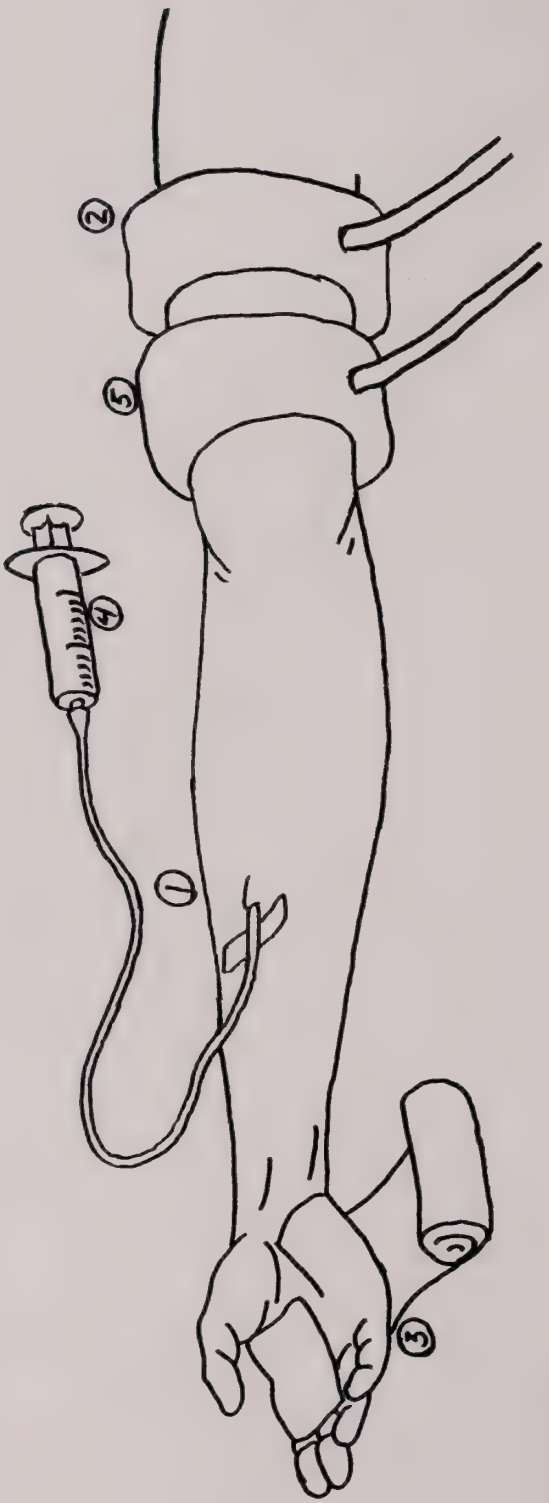
The tourniquet is placed on the upper arm as close to the axilla as possible and is connected to a source of pressure which must be adequate to overcome the systolic blood pressure. In isolated instances where this has not been done it has proven to be a serious hazard to the technique of regional anesthesia. The systolic blood pressure should be known before the tourniquet is inflated.

Step No. 3.

The arm is then elevated so that the blood will drain by gravity as a rubber bandage is placed to help squeeze the residual blood from the extremity. After the arm has been completely wrapped with the rubber bandage (Martin or Esmarch) to include even the upper tourniquet, the tourniquet should be in-

*Presented at the Big Mountain Medical Ski Conference January, 1968, in Whitefish, Montana.

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Figure

flated to a pressure above the systolic blood pressure. The rubber bandage is then removed and the arm laid down in the position for surgery.

Step No. 4.

At this time a syringe filled with the anesthetic agent is attached to the previously placed intravenous tubing for the purpose of injecting the agent slowly into the now collapsed veins. If at this time the needle should become dislodged from the vein, it is quite difficult to reinsert it in the collapsed vein and the procedure will probably have to be re-started. If the needle remains properly in place, the veins fill slowly. If they do not fill, then an adequate volume of anesthetic solution has not been used to produce acceptable anesthesia for the surgery involved.

The onset of anesthesia should be almost immediate.

Step No. 5.

In this last step, we now put a second tourniquet below the first. This tourniquet is, of course, being placed in an anesthetized area of the arm and when inflated will cause significantly less pain and discomfort than the upper tourniquet. Patients seldom tolerate the tourniquet for much more than 20 or 30 minutes without giving large voice to the complaint of pain involved. For this reason the second tourniquet below the upper one is now inflated and used to produce ischemia to the limb for the remainder of the operation.

Comments

In the recent literature a great deal of work has been done regarding the mode of action of intravenous regional anesthesia and what the long-term effects may be.

Volume and Dosage

Many individuals have been using this technique with different agents and volumes of solution. The general consensus is that it takes about 40 ml. of a solution to give adequate anesthesia in an adult arm and approximately 100 ml.[7] for an adult leg. The only anesthetic agents that seem to cause any degree of difficulty in this technique are 2-chloroprocain because of thrombophlebitis which may be associated with its use;[1] and although this is

not absolute contraindication, the formation of methemoglobin[3] following the use of prilocaine has been postulated as a hazard in the elderly patient for intravenous regional anesthesia.[6] Xylocaine (0.5%) injected in the previously recommended volumes gives adequate anesthesia for nearly all surgical techniques. Occasionally, with this concentration of agent a patient may retain some motor control and probably will feel some bone pain if extensive work is being done on the bones, such as insertion of artificial metacarpal phalangeal joints. To alleviate these problems, a higher concentration of anesthetic agent may be used in anticipated cases, but it must be realized that this also increases the possible toxic effects when the tourniquet is released.

Duration of Anesthesia

Most anesthesiologists feel that this technique should be limited to procedures that can be completed within two hours because of the restriction of arterial blood flow to the extremity. However, prolonged intravenous regional anesthesia for up to four hours[1] has been described in the literature by the technique of deflating the tourniquet after one to one and a half hours and a few minutes later reinflating it and then injecting one half the initial dose of local anesthetic. This may, of course, produce some discomfort during the time the tourniquet is deflated.

Circulatory Anesthesia

One of the major problems that has developed with intravenous regional anesthesia has been the problem of tourniquet release and consequently the release of perhaps large amounts of anesthetic agent into the circulation which, of course, will very rapidly reach the brain. Many studies of blood levels[4] of local anesthetics following the release of the tourniquet have been reported and indicate that peak concentrations are usually achieved at about five minutes after release. Approximately 15 to 30% of the local anesthetic injected into the isolated limb is found to reach the systemic circulation upon immediate release of the tourniquet. It has also been noted that the blood level of local anesthetic achieved after release of tourniquet in patients receiving regional intravenous anesthesia was less than the blood level of local anesthetic in patients receiving axillary, brachial plexus, lumbar epidural or caudal block.[4]

Mode of Action

It is thought that xylocaine or any other anesthetic agent in intravenous regional anesthesia travels out of the vascular space and through the tissues to reach the nerves or nerve endings themselves.[5] One study showed that intravenously injected procaine and xylocaine reduced nerve conduction in experimental animals in small but not in large-diameter myelenated axons. Since pain is conducted in the small myelenated axon and in some non-myelenated axons, this would give adequate cause for the pain relief achieved by intravenous regional anesthesia.[2]

Summary

The technique of intravenous regional anesthesia is described and recommended for use by general surgeons and others doing general medical and surgical work. The technique is nearly 100% successful if properly administered and complications are few and easily avoided. The safety of the technique is described and references to recent works in the literature show that the blood levels following this are certainly no greater than after other regional anesthetic techniques. Although we are not certain at this time of the exact mechanism of action of intravenous regional anesthesia, some of the more recent and plausible theories have been alluded to in this paper.

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Boys will be boys, and so will a lot of middle-aged men.—Kin Hubbard

Shakespeare: Diseases

Syphilis*

Timon was a wealthy noble Athenian who became disillusioned with the world because of its numerous evils and vices: war, prostitution, and particularly, human perfidy and corruption. Before his cave of self-imposed exile he had been approached by Alcibiades, the Athenian general, and his mistresses, who unashamedly confessed that they would do anything for gold. They pressed Timon for money until he became so incensed that he commanded them to betake themselves away, upbraiding them harshly for their venality and impudence.

Where else could be found a more devastating description of the ravages of syphilis than Timon's excoriating charge to the two prostitutes who solicited him for gold?

Consumption[1] sow
In hollow bones of man: strike their sharp shins,[2]
And mar men's spurring.[3] Crack[4] the lawyer's voice,
That he may never more false title plead,
Nor sound his quillets[5] shrilly; hoar[6] the flamen[7]
That scolds against the quality of flesh,
And not believes himself; down with the nose,
Down with it flat; take the bridge quite away[8]
Of him, that, his particular[9] to foresee,
Smells from[10] the general weal; make curled-pate ruffians bald,
And let the unscarred braggarts of the war
Derive some pain from you; plague all;
That your activity may defeat and quell
The source of all erection. Timon of Athens IV, III

[1]Any form of wasting disease.
[2]Cause painful nodes on their shins.
[3]Weaken their ability to apply spurs to their horses; there may be a sexual innuendo here.
[4]Cause venereal ulcerations of the larynx.
[5]Specious quibblings.
[6]Whiten with disease spots.
[7]Priest.
[8]Saddle nose of syphilis.
[9]Personal interest.
[10]Loses the scent of.
*See page 802, Creeping Death.

To say what you mean without ever offending people is usually to say what you mean without making them believe you mean what you say.—James Hilton

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Senior Peers

I have found no differences that are absolute between Eastern and Western life except in the attitude toward age. In China, the first question a persons asks the other on an official call is: "What is your glorious age?" If he replies apologetically that he is 23 or 28, the other generally comforts him by saying that he still has a glorious future, and that one day he may become old. Enthusiasm grows in proportion as the gentleman is able to report a higher and higher age, and if he is anywhere over 50, the inquirer drops his voice in humility and respect. People actually look forward to the celebration of their 51st birthday.—Lin Yutang

Coarctation of the Aorta in Veterans

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DURING A 19-year period (1948-1967), 18 veterans with coarctation** of the thoracic aorta have been admitted to the Veterans Administration Hospital.

Diagnosis

The detection of coarctation of the aorta in the young adult is generally considered to be relatively straightforward, most frequently made possible by the finding of a discrepancy in pulse strength and/or pressure between the upper and lower extremities. Other common findings are the occurrence of a bruit over the course of the thoracic aorta or intercostal vessels, x-ray findings of a prominent aortic knob or left subclavian artery, or rib erosion in the intercostal artery groove. Abdominal aortic coarctation or aortic occlusion secondary to arteriosclerosis, particularly in the older patient, also enters into the differential diagnosis; and appropriate procedures such as aortography may be indicated and are generally performed in most instances of suspected coarctation in recent years.

Despite the relative ease with which aortic coarctation can be diagnosed on physical findings, symptomatic coarctation of the aorta may go undetected for many years. All of our patients had been examined on several occasions, and some had been rejected for one service but subsequently accepted for another. Two had passed fairly detailed medical examinations and qualified to serve as pilots. Another served in the Marine Corps for five years and still another in the Army for six and one-half years. Several had been unduly penalized for suspected malingering because of their inability to participate in physical activities due to leg fatigue or to syncope or headaches associated with increased activity. Similar observations have been made by Sellars and Hobsley,[1] who described accidental discovery of coarctation in school children and in adults who were army commandoes, champion swimmers, and boxing

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**See Test Your Word Score Page 797.

competitors.

Coarctation of the aorta is generally considered incompatible with a normal life span. The average age of death in patients with untreated coarctation is in the mid-third decade of life[2]. Coarctation endangers life because of hypertension and its sequelae, such as aortic rupture, cerebrovascular accident, congestive failure, valvulitis, and endocarditis[3]. The occurrence of bicuspid aortic valve in 30 to 40 per cent of patients with coarctation has long been known. Such valves are apparently vulnerable to bacterial infection, and probably more so in hypertensive patients.

Indications for Surgery

The indications for and the technical considerations for the surgical treatment of aortic coarctation are now well recognized and have become standardized[4,5]. Many centers have reported on series consisting of hundreds of cases with a very low mortality rate. The most favorable period for correction of the coarctation is around the ages of seven to 15 years, when the aorta will have attained such size that even if the anastomotic site did not grow appreciably there would be no relative stenosis later in life. Correction during an earlier period or in infancy may, however, be necessary if cardiac failure cannot be controlled or if hypertension becomes severe. Because of secondary changes in the aorta surgical correction tends to be more difficult in older patients, particularly in those beyond the third decade of life. These dangers are now largely minimized by the utilization of either bypass, end-to-end, or patch grafts of prosthetic arterial substitutes.

Physical and X-Ray Findings

In our series the ages ranged from 19 to 60 years, with the majority in the 20 to 35-year range (Table). All have had one or more

TABLE
COARCTATION OF THE AORTA IN VETERANS

Age When Admitted	Preop Blood Pressure	Date of Operation	Years Followed
20	164/90	4/6/49	1 yr.—BP 145/70—Then moved to Neb.—Present status unknown.
24	170/95	2/25/50	10 yrs.—BP 150/76—Then moved to Calif.—Present status unknown.
27	180/98	3/8/51	16 yrs.—BP 150/70—Working as a carpenter.
29	190/130	7/12/51	12 yrs.—BP 114/80—Present status unknown.
32	210/120	2/19/54	9 yrs. BP 142/82—Worked as a painter—Present status unknown.
29	168/106	7/2/54	13 yrs.—BP 130/80—Working as a bookkeeper.
45	160/110	8/29/55	Died 11 months postop in another state. Diagnosis on death certificate—coronary occlusion.
30	156/90	9/15/55	8 yrs.—BP 120/70—Then moved to Calif.—Last heard from in 1963—Current status being sought.
19	160/80	3/13/56	11 yrs.—BP 110/60—Working as a mechanic.
31	180/90	9/9/57	10 yrs.—BP 154/72—One year postop—Now living in Calif. Current status being sought.
35	190/110	2/15/61	7 yrs.—BP 160/90—Three months postop—Working as manager of paper firm—Recent BP being sought.
36	160/90	4/3/61	7 yrs.—BP 135/80—Working as a farmer.
30	150/80	3/8/63	5 yrs.—BP 108/70—Working as a barber.
43	200/110	12/16/63	4 yrs.—BP 142/90—Working as a farmer.
37	150/80	12/2/66	1 yr.—BP 130/70—Working as heavy equipment operator.

Patient, Age 34, BP 164/92, Refused operation and left hospital in 1950. Relatives report patient died in 1963 at age 47, cause unknown.

Patient, Age 60, BP 200/96, First seen in 1955. Operation not done due to old age. BP 196/58 in 1960. Died at age 76 of congestive heart failure.

Patient, Age 37, BP 190/100, Refused operation and left hospital on 8/6/57. Present status unknown.

symptoms of recurrent headaches, shortness of breath, chest pain, aching legs, claudication, and episodes of dizziness. Varying degrees of hypertension were noted, some discovered on routine physical examination for work or for insurance (Table). Systolic and diastolic bruits over the precordium and along the scapula were present in all. About one half of the group had bruits along the intercostal arteries; 15 had rib erosion. Other x-ray findings were prominent aortic knob and left subclavian arteries. Only five underwent studies such as aortography and cardiac catheterization.

Surgery

Surgical correction was done in 15 patients. Two patients declined operation and one, age 60, was considered a poor surgical risk with operation not advised; but he lived to be 76 years of age.

Excision of the coarcted segment and end-to-end anastomosis were performed in 14 patients; and one 43-year-old patient had a 4 × 2½ cm. diamond-shaped dacron patch applied after an incision into the coarcted segment and into the aorta above and below the constriction because of large thin-walled collateral and intercostal arteries and post-stenotic dilatation and sclerosis of the aorta. All had the adult type of coarctation; in two a small opening was found in the ductus arteriosis. All patients survived the operative procedure.

The long-term follow-up information is listed in the Table. One patient is known to have died, and two in the non-operative group are known to be dead. After a variable period of follow-up, four in the operative group have not been traceable, and one in the non-operative group is lost to follow-up. Recent information is available in the remaining ten patients: they are well and working. All have responded favorably to fall in blood pressure, some more significantly than others. Symptomatic relief was also reported in all of the patients. Femoral and leg pulses became normal.

Summary

Experience with management of coarctation in 18 veterans is reviewed. This series is of some interest because it represents a group in whom the lesion eluded detection despite examination for physical fitness. More importantly, however, this group shows that coarctation in the adult may be excised safely with a favorable symptomatic response and lowering of the blood pressure.

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History

Charles A. Beard, the historian, was asked: "What lessons have you learned from all the history you have known?" He replied:

"1. When it gets darkest, the stars come out.

"2. When a bee steals from a flower it also fertilizes it.

"3. Whom the gods would destroy, they first make mad with power.

"4. Though the mills of God grind slowly, yet they grind exceedingly small."*

*Jacob Braude: Speaker's Encyclopedia.

DERIVATIVELY SPEAKING

Abdomen—possibly from Latin *abdere* (to hide)

Everything is simpler than you think and at the same time more complex than you imagine.—Goethe

The Heart Besieged

A young woman was brought in with a chest wound. She was hit from a pistol twenty minutes before, and her condition was serious. The surgeon found a tiny hole in her chest, but no second hole to show that the bullet had left the body. There were unmistakable signs that it had lodged itself in the heart or near it. The uncertainty of its exact location had the greatest bearing on what came after. The chance of saving the woman hinged on the hope that the bullet was embedded somewhere outside the heart.

The operation began. The surgeon exposed the heart. The wound was in its front wall, in the region of the right ventricle. The surgeon sutured it, and in making the final stitch his fingers encountered a solid object in the heart muscle. The bullet had penetrated the front wall, passed through the cavity of the ventricle, and lodged itself in the back wall of the heart.

That was just what the surgeon had feared most. To reach and extract the bullet he would now have to incise the wall of the ventricle. But that would mean a second wound to a heart muscle already damaged and copiously flooding the site of the operation with blood. Moreover, the surgeon would have to manipulate on the back wall of the ventricle, which was hidden from view. In that day it all appeared virtually impossible. To top it all, the bullet was lodged in the immediate neighborhood of the descending branch of the right coronary artery. Utmost care was required to avoid damage to this vital vessel.

The life of the patient hung on a thread, as it were, which grew slimmer and slimmer with every passing second. But the surgeon hesitated only for an instant. The operation continued. He drew out the heart as far as it would go, transfixed the heart muscle with two sutures, and cut the back ventricle wall. The cut was made in the direction of the bullet, opening access to it.

The silence of the operating room was soon broken by the sound of metal striking glass. The doctor had extracted the bullet and dropped it into a bowl. The operation ended happily.

That was how Manteufel, a Russian surgeon, made medical history in Yuriyev on September 12, 1905.*

*L. Fridland, M.D.: The Achievement of Soviet Medicine, 1961, edited and translated by W. Horsley Gantt, M.D.

A Jaw Dislocation

Gruelling as the ambulance work was, it always provided a welcome escape from the tense situation within the hospital, and sometimes the call would have its humorous aspects. One day a worn-out old woman with a grievance was at last having her day in court, letting the judge know all about it. As she got deeply into her story her excitement rose. She was finally gesticulating and shrieking with her mouth wide open striving for even greater eloquence when her jaw clicked. And there she was, poor thing, in agony with a dislocation, in greater mental agony that she had been silenced in her great moment.

A hurry call brought me from the hospital to the courtroom and there surrounded by fascinated onlookers, I was fortunate enough to be able to reduce the dislocation quickly. Another click and her jaw bone was back in place and then the torrent of words started right in, just where she had left off. As I went from the courtroom she was still going strong, and somehow I believe she may have won her case.*

*Emily Barringer, M.D.: Memoirs of a Lady Ambulance Surgeon, Bowery to Bellevue, 1950.

Neointimae

Smooth Muscle Cells in Replacement Teflon Prosthetic Grafts

T. SHIMAMURA, M.D.*
Vermillion, South Dakota

T. KAWAKAMI, M.D.**
A. C. BEALL, M.D.†
Houston, Texas

SMOOTH MUSCLE cells have not been observed by the extensive study on neointima‡ (Figure 1) of human Dacron arterial prostheses reported by DeBakey et al.[1] However, they have been demonstrated in the neointimae of arterial prostheses in the baboon[2] and in young growing pigs.[3] We are reporting the observation of morphologically characteristic smooth muscle cells in neointimae of canine infrarenal caval replacement Teflon prostheses.

Method

The infrarenal caval segment of five centimeters in length was replaced with a woven Teflon prosthesis in nine adult female dogs. At the same time, a side-to-side anastomosis was created between the 1-to-1.5 centimeter long incisions that were made in the wall of the right femoral artery and vein.[4,5] The femoral vein was ligated immediately distal to the fistula, and a collapse of the lumen was prevented by placing three stainless steel rings around the external surface of the prosthesis.[6] Four out of nine cases showed widely patent lumen until the time of their sacrifice by intracardiac injection of pentobarbital sodium at 26, 34 and 36 weeks (two cases) after the operation. The neointimae of only these four cases was studied. Of the excluded five dogs, two were killed at two and three weeks respectively without occlusion or stenosis of the lumen. The remaining three were killed in earlier phases of the experiment because of an occlusion or stenosis of the lumen.

Parts of the neointimae from the central segment of graft of these dogs killed at 34 and 36 weeks (one case) were fixed in Mil-

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Reprint requests to Department of Pathology, University of South Dakota, Vermillion, South Dakota 57069 (Dr. Shimamura).

‡See Test Your Word Score Page 797.

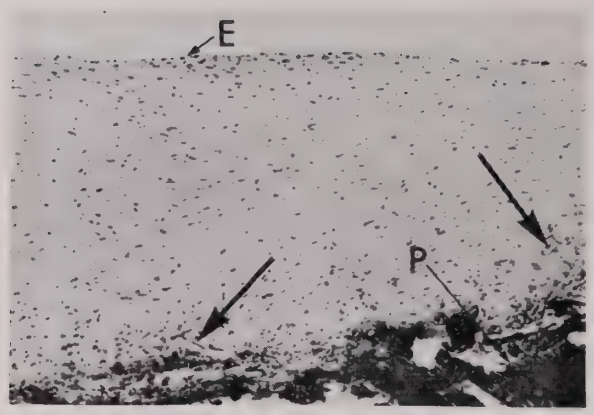


Fig. 1—A single layer of endothelial cells (E) lines the luminal side of the tissue. Immediately adjacent to the prosthetic material (P) is a mild foreign body reaction. The arrow indicates newly formed vasa vasorum. Hematoxylin and eosin stain. Mag. 45X.

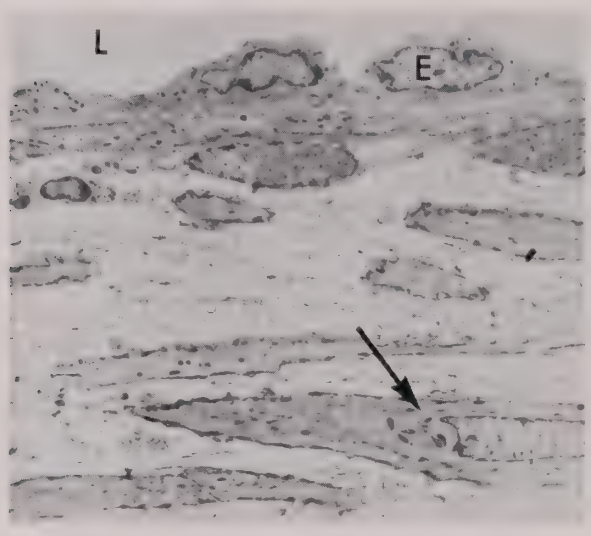


Fig. 2—Many smooth muscle cells are seen in parallel arrangement to the endothelial cells. L: vascular lumen. E: endothelium. Mag. 3300X.

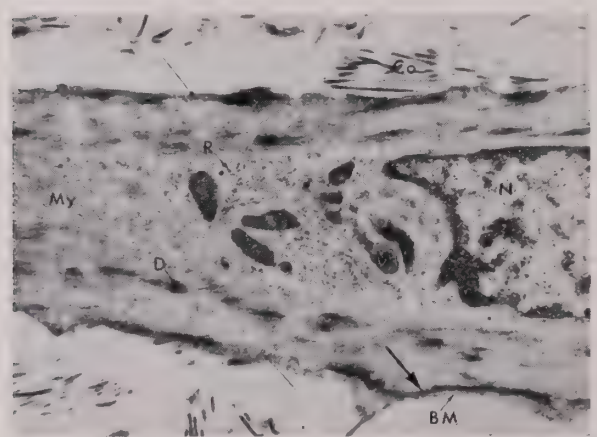


Fig. 3—Smooth muscle cells showing characteristic myofilaments. D: focal cytoplasmic electron dense area. M: mitochondria. N: nucleus. R: ribosomes. BM: basement membrane-like material. Co: collagen fibers. Mag. 25000X.

lonig-buffered[7] osmium tetroxide for one hour, dehydrated and embedded in a half-and-half mixture of Epon and Araldite. Thin sections were cut on a Porter-Blum microtome, double-stained with lead citrate[8] and uranyl acetate, and examined with an RCA-3G electron microscope. The remaining tissue from the four cases was fixed in 10% neutral formalin, embedded in paraffin, sectioned at a thickness of 6 microns and stained with hematoxylin and eosin for light microscopy.

Results

Endothelial Cells

The inside walls of these four prostheses with widely patent lumens were lined by a thin layer of semitranslucent gray smooth glistening tissue. The light microscopic section of the tissue showed fibrous connective tissue covered by a delicate single layer of endothelial cells (Figure 1).

Smooth Muscle Cells

By electron microscopy, morphologically characteristic smooth muscle cells were observed within the fibrous connective tissue (Figure 2). These cells were spindle-shaped, with abundant parallel myofilaments, which often appeared condensed to form electron-dense foci in the cytoplasm. The cell borders showed many vesicles. Nuclei were located centrally; and small numbers of mitochondria, ribosomes, and traces of rough-surfaced endoplasmic reticulum were seen in the paranuclear area. These cells were frequently surrounded by a basement membrane-like material (Figure 3).[9,10]

Connective Tissue

Ingrowth of connective tissue from the outside areolar tissue into the neointima through the tightly-knit prosthesis was not observed by us in the examination of the light and the phase microscopic sections.

Comments

We assume that the smooth muscle cells either grew from the line of anastomotic sites toward the center of the prosthesis or originated from cellular elements of the blood. It has been reported that the new inner layer which forms in the prosthesis proceeds from the lines

of anastomosis toward the center and is able to cover the entire inner wall if the length of the graft does not exceed 4 cm.[11] We are uncertain whether or not the smooth muscle cells will similarly appear in the central part of the woven Teflon replacement caval prosthesis of a much longer segment.

Summary

The neointimae of long-term patent canine infrarenal caval Teflon replacement prostheses were found to have endothelial cells and smooth muscle cells. The smooth muscle cells were present as the major cellular component in these neointimae.

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Hunter's Deer Antler Experiment

In the most roundabout way, an animal experiment sometimes led him to a new principle in human surgery. Once while studying the growth of antlers in deer, Hunter found that if he tied off the artery to the head on one side the antler became cold, but in a few weeks the circulation was completely restored. Autopsy showed that the blood had been shunted through other blood vessels.

Many years later he applied this observation to a patient with a clot inside a large pocket of a stretched and bulging artery in the knee. The customary treatment was to tie the vessel above and below the clot, and then scoop the clot out of the bulging pocket (aneurysm). The procedure was fatal so often that amputation was considered safer. Hunter recalled the experiment with the deer's antler. He tied the large artery in the triangular space (now called Hunter's canal) between three muscles above the knee, shutting off that branch of the circulation. Within six weeks the patient was well, his leg having been nourished by the blood shunted from neighboring connecting vessels. Since then this procedure for treating aneurysm has saved many a limb as well as life.*

*Sarah R. Riedman: Masters of the Scalpel, 1962.

Silverweed

Silverweed resists the fits of agues, is said to break the stone and is good to cool inflammation in the eyes, as else to take away all discolourings of the skin and to cleanse it from any kind of depredation.—Salmon

Honorable Mention

The May issue* carried the announcement of the MINNESOTA MEDICINE Medical Writing Honor Award winner for 1968 and also the three Honor Certificate winners for excellence in medical writing.

Now the Board of Editors proudly lists in this issue the authors who received honorable mention for their presentations:

Name	*Manuscript*	*Issue*
J. M. B. Bloodworth, Jr., M.D. *Madison, Wisconsin*	*"Renal Vascular Disease Associated with Diabetes Mellitus"*	*March*
Frederick C. Goetz, M.D. *Minneapolis*	*"The Regulation of Insulin Secretion"*	*March*
Carl W. Laymon, M.D. *Minneapolis*	*"Nodular Disorders of the Legs"*	*July*
J. L. McKelvey, M.D. *Minneapolis*	*"The Abortion Problem"*	*January*
Gerald M. Needham, M.D. and James E. Wenzl, M.D. *Rochester, Minnesota*	*"Enteropathogenic Escherichia Coli in Children"*	*September*
Willard C. Peterson, Jr., M.D. *Minneapolis*	*"Fluorescence-Selected Medical Aspects"*	*May*
Warren J. Warwick, M.D. *Minneapolis*	*"Cystic Fibrosis—Nature and Prognosis"*	*July*
Charles B. Wilson, M.D. and Horace A. Norrell, Jr., M.D. *Lexington, Ky.*	*"Management of Head Injuries"*	*February*

The Editors again wish to express their thanks and applause to all of the above distinguished authors.

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* See page 653.



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There are more than 30 million people in America who are overweight. During the next year, you probably will see more than 1,000 of them in your own practice.

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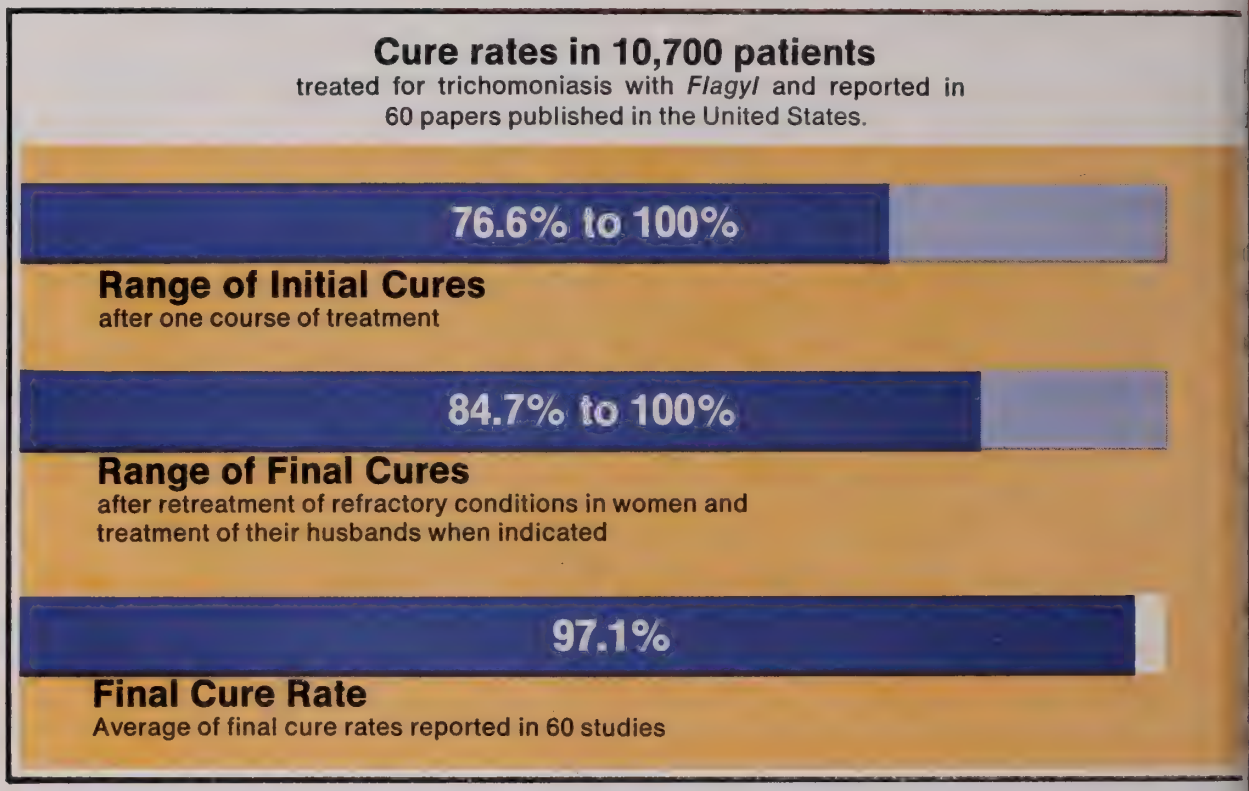
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Indications: Flagyl is indicated only in the treatment of trichomoniasis in both men and women.

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Precaution: Complete blood cell counts should be made before, during and after therapy, especially if a second course is necessary.

Side Effects: Infrequent and minor side effects include nausea, metallic taste and furry tongue. Gastrointestinal disturbances, flushing and headache sometimes occur, especially with concomitant ingestion of alcohol. The taste of alcoholic beverages may be altered. Other effects, all reported in an incidence of less than 1 per cent, are diarrhea, dizziness, vaginal dryness and burning, dry mouth, rash, urticaria, gastritis, drowsiness, insomnia, pruritus, sore tongue, darkened urine, anorexia, vomiting, epigastric distress, dysuria, depression, vertigo, incoordination, ataxia, ab

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n clinical practice an occasional uncooperative or drug-sensitive patient r spouse makes 100 per cent cure of trichomonal vaginitis in large series f patients difficult.

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Sixty papers[1] published on the use of Flagyl in trichomoniasis in the Jnited States and comprising a total of 10,700 patients have been evalu- ted. In thirty of the papers it was declared that all patients adequately ollowed and treated were free of trichomonal infection.

Analysis of all of these papers shows that the incidence of cures for he *initial* course of therapy ranged from 76.6 per cent to 100 per cent. The cure rates after retreatment of female patients and treatment of their usbands when indicated ranged from 84.7 to 100 per cent. The average inal cure rate reported in all investigations was 97.1 per cent.

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dominal cramping, constipation, stomatitis, numbness or paresthesia of an extremity, joint pains, confusion, irritability, weakness, cystitis, pelvic pressure, dyspareunia, fever, polyuria, incontinence, decreased libido, nasal congestion, proctitis and pyuria. Elimination of trichomonads may aggravate candidiasis.

Dosage and Administration: In women: one 250-mg. oral tablet three times daily for ten days. A vaginal insert of 500 mg. is available for local therapy when desired. When used, one vaginal insert should be placed high in the vaginal vault each day for ten days; concurrently two oral tablets should be taken daily.

In men: When trichomonads are demonstrated, one 250-mg. oral tablet twice daily for ten days in conjunction with treatment of his female partner.

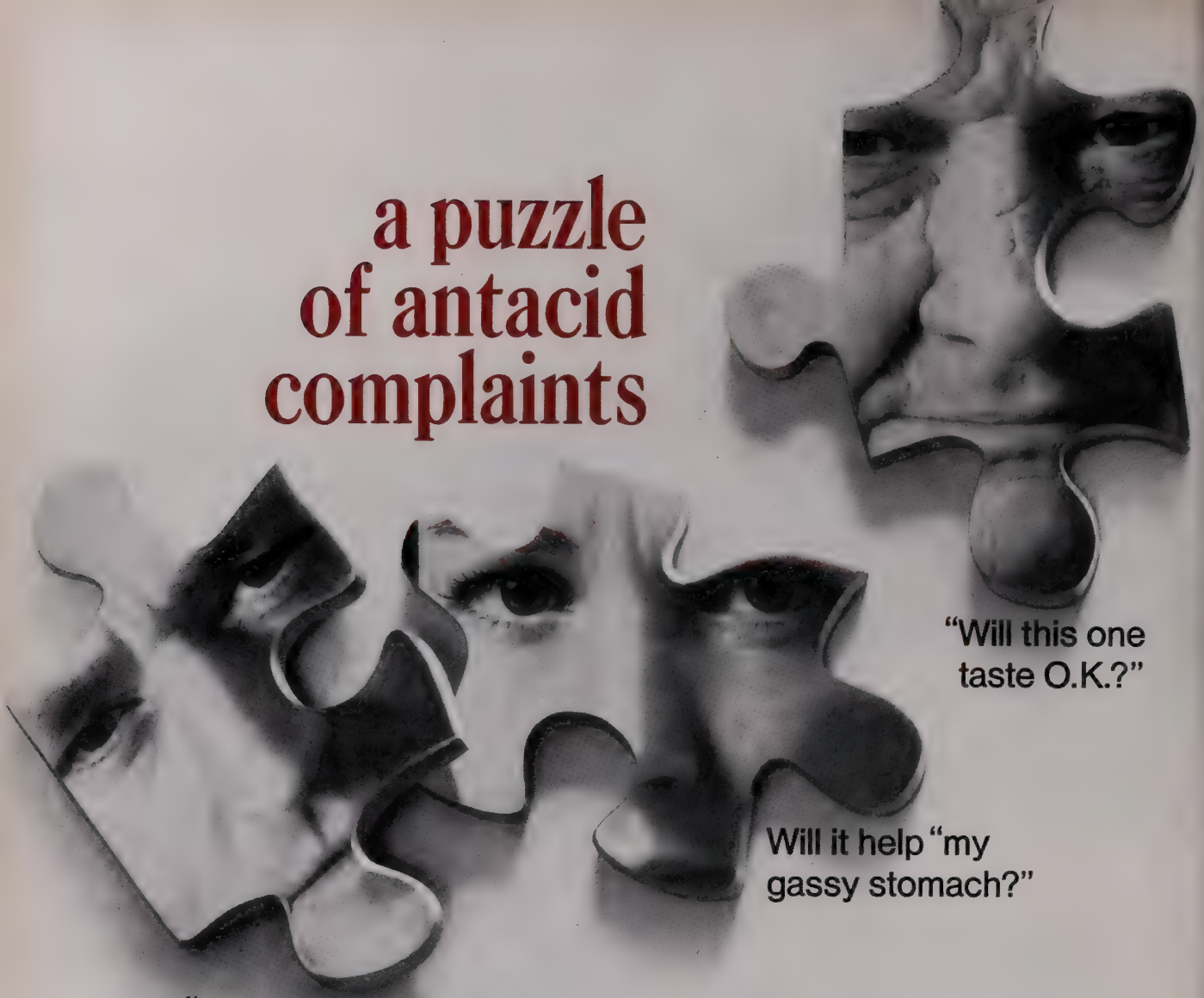
Dosage Forms: Oral tablets—250 mg.
Vaginal inserts—500 mg.

1. Complete list of references on request.

SEARLE

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Composition: Each Mylanta chewable tablet or teaspoonful (5 ml.) contains: magnesium hydroxide, 200 mg.; aluminum hydroxide, dried gel, 200 mg.; simethicone, 20 mg. Dosage: One or two tablets (well chewed or allowed to dissolve in the mouth) or one or two teaspoonfuls to be taken between meals and at bedtime.

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ATLAS CHEMICAL INDUSTRIES, INC.



Editorials

Minnesota Medicine Joins the 50 Year Club

VOLUME 1, No. 1 of MINNESOTA MEDICINE appeared in January of 1918. This same year 17 physicians whom we honor this year entered into the practice of medicine.

These physicians* received their 50-club pins at ceremonies last month at the Annual Meeting of the Minnesota State Medical Association in Rochester. This is a scintillating company of doctors whose work is now part of Minnesota history. Particularly distinguished are those great men who helped transform the medical school into the world-renowned institution of today.

Prior to 1918 "THE JOURNAL OF THE MINNESOTA MEDICAL ASSOCIATION" appeared as a section of the JOURNAL LANCET. The new MINNESOTA MEDICINE owned and controlled by the state organization ventured forth into the medical world under the editorship of Dr. Ernest T. F. Richards of Saint Paul, who no doubt wrote this "Salutatory" of MINNESOTA MEDICINE: "Now that the Minnesota profession has taken this step, it is a foregone conclusion that it will never regret it and will soon feel the value of the bond its own journal will make between its various component county and district associations, and above all the bond that will bind the entire membership into a more homogeneous whole. There is no better instrument to do this thoroughly than a mutual interest in the success of an undertaking." Subscription price was $2.00 per annum in advance, single copies 25¢, foreign countries $3.00 per annum. There have been three editors since Dr. Richards, namely: Dr. Charles B. Drake, Dr. Arthur H. Wells, leading up to our present Editor-in-chief, Dr. Carl O. Rice, who was a teenage boy with the American Expeditionary Forces in France in January, 1918.

The year of 1918 was one of glory for the United States with the troops coming home victorious from World War I in France, Belgium, and Germany. Woodrow Wilson was the man of the year who would lead the world out of purgatory into a democratic heaven.

Volume I of MINNESOTA MEDICINE is a mirror of the times and the following quotations are taken from it:

Tonsillectomy was near the zenith. "Joint, heart, kidney, goiter and glandular conditions show such marked improvement after tonsillectomy as to leave no doubt as to the source of infection." (Gillespie, N.H., page 21). However, not everyone agreed. "While

*See page 805.



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it may seem presumptuous and foolhardy in this enlightened medical age to question, it is my sincere belief that the profession has gone plum loco on the tonsil question, and that they are barking up the wrong tree. I regret that one of the latest fantasies in the treatment or prevention of rheumatism seems to have been found in tonsillectomy." (James, J.H., page 23). Doctor Charles N. Spratt said: "Like Banquo's ghost the tonsil question is ever before us and it is still unsettled. I divide my tonsil cases into two classes—those in which I make a diagnosis at the office from the appearance of the tonsil, and those in which we make a diagnosis over the telephone, or from what the patient tells me. The first variety is the large hypertrophied tonsil, diseased or not, and in the second variety one makes the diagnosis from the history, namely repeated attacks of tonsillitis or rheumatism."

Advertisement: "Good location, open for position. There is a splendid opening at South Shore, South Dakota, for a doctor who can run a small drugstore in connection with his practice."

Of General Interest: "Lt. Theodore H. Sweetser of Minneapolis, son of Doctor H. B. Sweetser, has been recommended for the British War Cross for bravery and devotion to duty near Paschendale on March 13. Lt. Sweetser attended to 40 gas victims although he was himself suffering from the poison gas." "Dean Wulling and his co-workers in the College of Pharmacy, University of Minnesota, during the past year prepared 28,000 half-pint bottles of tincture of digitalis. This constituted the complete supply of the drug used in the United States army."

"Some of you probably heard what Sir James McKenzie said in Chicago at the meeting of the American Medical Association. I heard him discuss effort syndrome, in which he brought out conclusively the fact that he was sorry the stethoscope had ever been invented, meaning by that, we have been paying too much attention to the morphology of the heart and not enough to its function." (Discussion by Doctor H. L. Ulric of a paper by Olga S. Hanson). Doctor Hanson's paper discussed the value of that new instrument—the electrocardiograph in cardiac diagnosis. Sir James' deprecatory remarks about the stethoscope in 1918 apply equally well in 1968 and could be extended to include the electrocardiograph whose evidence unsupported by symptoms can do more harm than good.

News From Abroad—"Dear Doctor Farr (Robert Emmet Farr). I thought you would be interested to know how I spent the leave which I have had in Blighty. I visited Professor E. Thompson (Edinburgh). He performed an excision of the rectum for carcinoma 2½ weeks after a permanent preliminary colostomy. He reported that since he made a permanent artificial anus and did not attempt to save the sphincter, his percentage of recurrence in rectal cancer was greatly reduced." (Stanley R. Maxeiner, Capt., M.C., U.S.A., page 70).

I also took part in the war effort, recalling after a half century the three-minute speech exhorting* fellow students at Harrison School in the fifth grade to buy liberty bonds.

Reuben Berman, M.D.
Minneapolis, Minnesota

*See Test Your Word Score Page 797.

Thought for Today

Thank God every morning when you get up that you have something to do which must be done whether you like it or not. Being forced to work, and forced to do your best, will breed in you temperance, self-control, diligence, strength of will, content, and a hundred other virtues which the idle never know.—Chas. Kingsley

"Undress," as George Herbert says, "your soul at night," not by self-examination, but by shedding, as you do your garments, the daily sins whether of omission or commission, and you will wake a free man, with a new life.—William Osler

Doctors think a lot of patients are cured who have simply quit in disgust.—Don Herold

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BRIEF SUMMARY/**Indications:** Ambar suppresses appetite and helps offset emotional reactions to dieting. **Contraindications:** Hypersensitivity to barbiturates or sympathomimetics; patients with advanced renal or hepatic disease. **Precautions:** Administer with caution in the presence of cardiovascular disease or hypertension. **Side Effects:** Nervousness or excitement occasionally noted, but usually infrequent at recommended dosages. Slight drowsiness has been reported rarely. See package insert for further details.

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Research*

With respect to the expenditure of public funds for the purpose of research in general, the federal government within recent years has assumed a major role and seems destined to play a larger and larger part as time goes on. By 1966 the federal share for research expenditures amounted to approximately 70% of the funds spent in this country on biomedical research. With the total national biomedical research program now having grown to a multibillion dollar enterprise, perhaps it is time to sit back and reflect on how judiciously this segment of the federal fiscal outlay is being managed, with a view toward implementing changes that would ensure the most fruitful return.

The Surgeon General of the Public Health Service recently stated: "Free scientific inquiry is the foundation upon which the entire complex rests." There is great wisdom in this statement and the message it bears deserves very thoughtful attention. Any attempt to improve the quality and the quantitative yield of research must give priority to considerations which will allow free scientific inquiry to operate unimpeded. Philosophical confidence in the humanitarian generosity of others must not relate the anticipated research productivity directly to the amount of fiscal outlay. Spectacular achievements often emanate from well thought out but poorly funded research programs. More lavishly supported programs may be unproductive because they are nourished by unimaginative minds or because there may be factors operating which act to restrict the talents of the researchers. Energies must be directed toward finding ways to unleash the creative genius of the scientific mind. Ideas are born of the minds of men and not of fiscal coffers.

In order to establish a research setting conducive to free scientific inquiry the investigator must be freed from the "political" aspects connected with research. Perhaps once a grant award is made to a researcher he should be invested with sufficient control over his funds, so that the direction of his program resides in his hands. He should be guaranteed continuity in the use of the funds over the entire period for which the grant award was made. Such assurances are essential to ensure productive use of research funds.

The artificial heart research program promises to become a multibillion-dollar federal undertaking. It is important that the system under which research is carried out in this country be carefully reviewed and overhauled prior to obligating such an immense portion of public funds. The time and effort taken in doing this will be rewarded by an improvement in the quality of research, not only in the artificial heart program, but in research programs generally.

Harold D. Kletschka, M.D.
Edson H. Rafferty, B.S. (M.E.)
Houston, Texas

Martin Wynyard, M.D.
Syracuse, New York

*See Editor'ss Soliloquy, page 799.

Tympanoplasty for Chronic Otitis Media

The literature in Otology from the earliest stages contains repeated references to efforts in eliminating disease from the ear while preserving its function. In the early stages, successful accomplishment of these aims was limited by the inability of the unaided eye to see the small structures of the ear sufficiently well to allow conservative surgery. During the past quarter century, increasing use of magnified vision in otologic surgery has allowed increasing refinements in techniques. The use of magnifying loupes was of great benefit, but the degree of magnification was limited. Development of the surgical microscope, which allows magnification up to 40 power with adequate working distance, gave great impetus to the

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Average adult dosage: 2 tablets four times daily, given at least one hour before, or two hours after meals.
Contraindications: History of hypersensitivity to any component.
Warning: If renal impairment exists, even usual doses may lead to liver toxicity. Under such conditions, lower than usual doses are indicated and, if therapy is prolonged, serum level determinations may be advisable. Hypersensitive individuals may develop a photodynamic reaction to natural or artificial sunlight during use. Individuals with a history of photosensitivity reactions should avoid direct exposure while under treatment, which should be discontinued at first evidence of skin discomfort.
Precautions: Some individuals may experience drowsiness, anorexia, and slight gastric distress. If excessive drowsiness occurs, it may be necessary to increase the interval between doses. Persons on full dosage should not operate any vehicle. Use may result in overgrowth of nonsusceptible organisms. If infections appear during therapy, appropriate measures should be taken. Infections caused by beta-hemolytic streptococci should be treated for at least 10 full days to help prevent rheumatic fever or acute glomerulonephritis. Use of tetracycline during tooth development may cause discoloration of teeth.
Adverse Reactions: Gastrointestinal—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin—maculopapular and erythematous rashes (a case of exfoliative dermatitis has been reported); photosensitivity; onycholysis and discoloration of nails (rare). Kidney—rise in BUN, apparently dose related. Hypersensitivity reactions—urticaria, angioneurotic edema, anaphylaxis. In young infants, bulging fontanels following full therapeutic dosage has been reported. This has disappeared rapidly when drug was discontinued. Teeth—dental staining (yellow-brown) in children of mothers given tetracycline during the latter half of pregnancy and in children given the drug during the neonatal period, infancy, and early childhood. Enamel hypoplasia has been seen in a few children. Blood—anemia, thrombocytopenic purpura, neutropenia, eosinophilia. Liver—cholestasis (rare), usually at high dosage. If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy.

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350-8

development of reconstructive surgery of the ear. Progress has been particularly rapid during the past decade since the use of the surgical microscope has become widespread. When one considers that the ossicles of the ear are the smallest bones of the body and that their measurements in many instances are in fractions of a millimeter, one can understand the extreme care necessary while operating in this region. This care is feasible when visualization of the area is adequate. Dr. Guilford* is one of the leaders in the development of otologic surgery in the United States. Many of the techniques in wide use are the result of his efforts and experience.

As a result of the improvements in surgical techniques, surgical treatment of chronic disease of the middle ear is now advised at a much earlier stage than it was a few years ago. If adequate surgical treatment is given prior to destruction of the middle-ear structures, the risks of complication and of permanent hearing loss are greatly reduced.

Kinsey M. Simonton, M.D.
Rochester, Minnesota

*Guilford, F. R.: Tympanoplasty for Chronic Otitis Media. Minnesota Med. 50:891, 1967.

Maternal Rubella

The Need for Early Identification of Hearing Loss.

As is well known, maternal rubella in the first trimester of pregnancy can cause multiple congenital defects. Outstanding examples of these defects are sensorineural hearing loss, cataracts, heart defects and mental retardation. Throughout the nation, health care professionals are becoming aware of the frightening number of these defects resulting from the rubella epidemic of the early 1960's.

There is a great need for early identification of the children with a congenitally acquired hearing defect. The sooner the hearing loss is recognized, hopefully by age six months to one year, the better chance the child has of obtaining maximum benefit from a structured habilitation program for language and speech development.

Recent advanced otolaryngologic and audiologic diagnostic techniques have made early identification of hearing loss in very young children a reality. For example, cortical audiometry* in conjunction with standard otolaryngologic and audiologic procedures allows an early and accurate estimation of the hearing in these children. With this information an early program can be started; amplification can be so utilized that these children are not deprived of critical auditory input in the developmental years of language and speech. All physicians who have contact with rubella infants must be aware of the necessity for early hearing examination. Observation without definite diagnosis throughout the critical age period of twelve to twenty-four months when language perception and speech should be developing is bad medical practice. Children so neglected will have to compensate later for the time interval when they lacked auditory input. Unfortunately, some children never completely recover this lost opportunity.

Jerome A. Hilger, M.D.**
Craig O. Linnell, Ph.D.**
St. Paul, Minnesota

*See Test Your Word Score Page 797.

**Otolaryngology Clinic & Professional Associates.

Etiology of Skin Cancer

The terms "cancerous," "benign," "malignant" are used glibly and often. In fact, no entirely satisfactory definitions are applicable to all the varieties of tumors and tumor-host interactions.*

The skin should be an ideal tool with which to clarify concepts of cancer. The most accessible "organ" of the body, it is also prone to develop malignant tumors. This may relate to its role as protective barrier against the surrounding environment.

*See Peterson, W. C., Jr.: Precancer and Cancer of the Skin. Minnesota Med 51:483, 1968.



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No one, as yet, understands how environmental factors induce malignant change. Actinic keratoses, leukoplakia, and arsenical keratoses are examples of "premalignant" skin tumors which may be produced by environmental factors. "Premalignant" indicates a significant probability that these benign tumors will become malignant. Estimates of this probability vary but are mostly in the range of 20 to 30%. There is no sharp line between the malignant and the benign lesion. Malignant transformation in these "premalignant" tumors probably begins in one cell, which then multiplies at a faster rate than the surrounding normal cells and displaces them. The transformed cells transmit the "malignant character" to daughter cells; therefore we may assume that a basic genetic change has taken place.

Study of genetic factors may help to delineate the causes of skin cancer. The nevoid basal-cell carcinoma syndrome, an autosomal dominant trait, affects several tissues. In the skin multiple basal-cell carcinomas develop at an early age. The clinical and histologic appearance of these tumors does not differ from the ordinary non-heritable basal-cell carcinomas. In xeroderma pigmentosa, a rare familial skin disease with an autosomal recessive mode of inheritance, extreme sensitivity to sunlight begins in early childhood. There follows severe degenerative changes in the skin with development of squamous-cell carcinomas, basal-cell carcinomas and melanomas.

Keratoacanthoma is a rapidly growing skin tumor which may be difficult to differentiate histologically from squamous-cell carcinoma. The nature of keratoacanthoma is not understood. Calling it a "pseudocancer" only clouds the issue. Is this tumor benign or malignant? Is containment and destruction of the tumor due to host factors, or to some intrinsic factor in the tumor itself, or to both?

The rising incidence of skin cancer may be due to an aging population and to increasing exposure to actinic and other forms of radiation. This makes further study and understanding imperative. Beyond this, study of skin cancer should help to illuminate tumor-host interactions and the effects of environmental and genetic factors.

Bruce J. Bart, M.D.
Minneapolis, Minnesota

Pharyngo-Esophageal Dysfunction

Dr. Kirchner's* discussion of pharyngo-esophageal dysfunction is indeed excellent. Inasmuch as he is a noted laryngologist, it is not surprising that his principal emphasis is on the pharyngeal and upper esophageal phases of deglutition. He stresses the importance of distinguishing organic lesions, such as tumors, strictures, and diverticula, from neurologic, neuromuscular, and functional disorders related to the hypopharynx and the cricoid sphincter. Dr. Kirchner describes the symptoms that characterize the various types of upper esophageal and pharyngeal dysphagia and the importance of accurate observation of the patient's behavior during deglutition. The findings on inspection of the throat are described in detail. In most cases, the nature of the disorder can be suspected from the history and clinical observations.

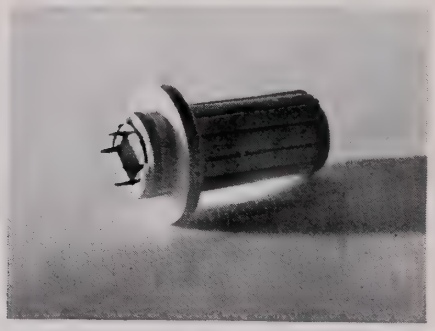
Dr. Kirchner calls attention to the role of manometric studies, which we have found so very useful in elucidating the physiology of deglutition and the mechanisms of the various neuromuscular disturbances of the esophagus and the esophagogastric sphincter. The techniques for making these determinations have been refined, and such manometric studies are now performed routinely in our evaluation of swallowing disorders. Although esophageal motility studies have been used primarily in the evaluation of disturbances of the esophagus and lower sphincter, they are indeed applicable to the upper sphincter and hypopharynx. Such disorders as "achalasia of the cricoid" and "the hypertensive cricoid sphincter" can be recognized with the pressure recorders that are used for these studies.

A brief reference was made by Dr. Kirchner to endoscopic examination of the pharynx and esophagus. Although such examinations are

*Kirchner, John A.: Pharyngeal and Esophageal Dysfunction. Minnesota Med 50:921, 1967.

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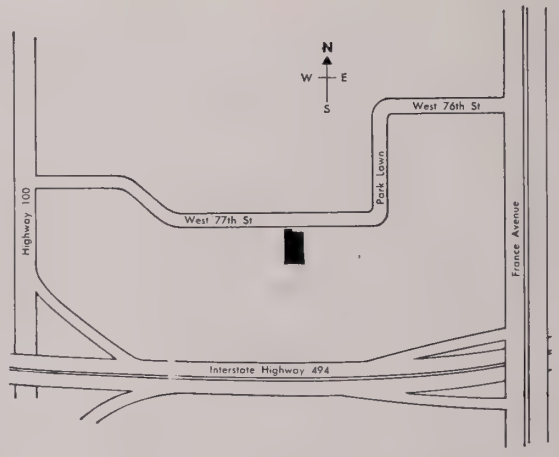
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essential to detect organic lesions, they are certainly of less value in the evaluation of neuromuscular disorders involving the esophagus and the sphincters. We have found that the passage of bougies over a previously swallowed thread is a valuable diagnostic technique in such neuromuscular disorders. The type of resistance that is encountered will help to determine the nature of the disturbance, and this procedure is sometimes very valuable in the treatment of various esophageal abnormalities.

Arthur M. Olsen, M.D.
Rochester, Minnesota

Test Your Word Score

Myelomeningocele— *spina bifida with protrusion of the cord and its membranes* (page 762).

Coarctation—*narrowing* (page 775).

Neointima—*new fibrous tissue lining the inside wall of a vessel prosthesis* (page 779).

Exhorting— *inciting by argument or advice* (page 789).

Cortical audiometry—*a computerized form of electroencephalogram audiometry* (page 793).

Elan vital— *the vital force of life* (page 799).

Electrophoresis— *the movement of particles in an electric field toward one or the other electric pole* (page 816).

Priory—*a religious house* (page 820).

Hebenon—*a poisonous substance probably derived from henbane or ebony* (page 828).

Lazar—*repulsive disease* (page 828).

Tetter—*vesicular skin disease* (page 828).

Hips—*pseudocarps (false fruit) of the rose* (page 838.).

Haws—*hawthorn berries* (page 838).

Creasses—*an obsolete word probably referring to certain portions of the neck* (page 838).

Burdock seed—*a coarse composite herb* (page 838).

Endotoxin—*a toxin elaborated within a micro-organism* (page 853).

When I was young I was amazed at Plutarch's statement that the elder Cato began at the age of eighty to learn Greek. I am amazed no longer. Old age is ready to undertake tasks that youth shirked because they would take too long.—W. Somerset Maugham



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The Editor's Soliloquy

Tiger by the Tail

The heart is a pump. It possesses no physiologic, endocrine, biologic function, as other vital organs do. Furthermore, it is without doubt biologically inferior to the life-sustaining blood which it propels throughout the body; and as an organ it is infinitely less complex than many of the other organs which it keeps alive by its relentless pumping action for an average of 68 years.

There are some mystical notions about the heart being the center of life—the citadel of the *elan vital*,* as it were, because when it stops beating, life terminates abruptly. If, however, its pumping function could be taken over by a mechanical apparatus, this surrogate organ might conceivably provide a few years' moratorium on death.

Since successful heart exchange between two homogeneous individuals receives and apparently requires no nerve connection to the recipient, future studies might well be directed to a pumping mechanism rather than a pumping muscle, thus eliminating the reflex autonomic obstacle as well as the sensitive moral issues involved. After all, non-reactive materials are already available for replacing diseased vessels, and the interposition of a mechanical pump should not constitute an insurmountable obstacle.

Kletschka et al.** have devised a prototype of a mechanical heart which is somewhat smaller than the chest cavity and does not destroy blood cells. It remains for him and his associates to perfect this model, reduce it to the size of a normal heart, install within it a long-lived or rechargeable power source and electric motor, and perhaps create a systolic-diastolic impulse with capacity to maintain a relatively normal blood pressure. It would appear that the mechanical difficulties of perfecting such an instrument would be far fewer and simpler than those involved in anticipating and controlling the numerous unpredictable biologic, physiologic and immunologic imponderables of installing and maintaining a muscular heart, whether homogeneous or heterogeneous.

Electroencephalographic tracings have demonstrated cessation of brain function even though the heart continues to beat and respiration is being artificially maintained. It is conceivable that under these circumstances many other bodily functions could continue as long as circulation is maintained. But without evidence of cerebral function should these other processes be continued? Heretofore, when the electroencephalogram has revealed no evidence of life in the brain, both the medical profession and the clergy have been content to consider the motor turned off.

Reliance on a donor entails too many complex problems: biologic, immunologic, physiologic, legal, social, moral and religious, when one is waiting for nothing more than a pump. This does not gainsay, however, that experimental studies should not be done on both homogeneous and heterogeneous heart transplantation, with all their variable and intangible somatic responses to the nth power. Unless an unforeseen breakthrough occurs or an unpredictable immunologic-biologic-physiologic phenomenon develops, it can be predicted that thousands of experimental hours and millions of dollars will be expended before the solution of a perfect heart transplant is obtained.

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*See Test Your Word Score Page 797.

**Kletschka, H. D., et al.: Artificial Heart. Minnesota Med 51:11 and 51:191, 1968. Also see page 787.

Nevertheless, studies should be conducted concurrently in all three of these areas: mechanical, homogeneous, and heterogeneous restoration of heart function, each study to be pursued freely and exhaustively.

Barnard and Shumway have already conducted independent clinical trials that have not been futile, despite their high mortality. Further clinical studies must be continued, but the public should not be allowed to become so optimistic by way of undue publicity as to expect revolutionary changes in the cure of cardiac disease within a decade.

Investigators will be flooded with volumes of praise and criticism; they will be simultaneously anathematized as fiends and eulogized as saints. They must be able to withstand the damaging effects of both. They must seek neither fame nor fortune. They must persevere single-mindedly despite frustration and failure and leave it to history to assess and evaluate their achievement.

History tells us that medical scientists have had a tiger by the tail before; true scientists live on, securely and honorably immortalized in medical annals, while the charlatans, the quacks and the pseudoscientists are interred with their fortune, their notoriety, and their bones.

Carl O. Rice, M.D.

Old Doc Hess says: She has to go to church on Sunday now and then just to keep even with those who go every Sunday and probably don't mean it.

President's Letter Continued from Page 757.

those who occupy a full-time position in a hospital as Directors of Medical Education or Directors of Department of Medicine or Surgery. These men, although they are for the most part academically trained, are more like the old time Clinical Professor, but unlike him they do not have the disadvantages of a burdensome practice. These Directors will have time for reading and research, and for teaching. They will be experts in Clinical Medicine and Surgery.

If there has been a misunderstanding between the full-time medical school teacher and the practitioner, there may be even more between the practitioner and the full-time hospital teacher. However, neither can get along without the other. If the medical staff resists the full-time surgeon, it will soon find the hospital deteriorating. If the full-time educator does not understand the problems of his staff, he too will suffer.

Let us hope that this new breed of educator will flourish and that the full-time medical school educator, the full-time hospital educator, and the profession itself can function together with patience and understanding. From this accord will result better medicine for all the people.

Wallace P. Ritchie, M.D., President
Minnesota Academy of Medicine

Remedies for Erysipelas

For erysipelas a liniment of bears' grease is used, that from the kidneys in particular; fresh calves' dung also, or cow-dung; dried goats' milk cheese, with leeks; or else the fine scrapings of a deer's skin, brought off with pumice-stone and beaten up in vinegar. Where there is redness of the skin attended with itching, the foam from a horse's mouth is used, or the hoof, reduced to ashes.—Pliny

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Primrose Leaves

Of the leaves of the primrose is made as fine a salve to heal wounds as any I know.
—Nicholas Culpeper



Curbstone Consultation

Central Venous Pressure

QUESTION: Monitoring of the central venous pressure has found its place as a very valuable method for the clinical management of patients. Can you outline some of the limitations in its use?

ANSWER: Even assuming that one uses the method in a technically proper manner there are certain limitations of which one should be aware. It is very valuable in assessing the relationship that exists between blood volume, cardiac competence, and vascular tone. However, it is important to bear in mind that a specific ventricular function curve exists for a particular circulatory state. For example, in a case in which the myocardium is compromised, a given central venous pressure will be associated with a smaller ventricular stroke work than in the case of a normal myocardium. Thus a venous pressure of 8 cm water in a normal heart may indicate the same balance between cardiac competence and effective blood volume as does a much higher venous pressure in a borderline compensated heart.

A healthy heart may decompensate with pulmonary edema at a lower central venous pressure than a diseased heart. Serial venous pressures are more valuable than isolated readings. The function of the right ventricle is more reliably assessed by the central venous pressure than that of the left ventricle. The central venous pressure may be misleading when hypovolemia coexists with (or even precipitates) cardiac failure with a rising venous pressure. The increased venous return may lead to improved cardiac function. Central venous pressure readings may also be unreliable when mechanical obstructive states exist, such as mediastinal compression from tumor masses, venous thrombosis, and cardiac tamponade. Changes in intrathoracic pressure such as occur in cases of flail chest, pneumothorax, hemothorax, or positive pressure breathing may result in changes in the central venous pressure in such a way that the readings no longer reflect a measurement of the underlying state of the heart, blood volume, or vascular tone.

Harold D. Kletschka, M.D.
Houston, Texas

He was a simple soul who had not been introduced to his own subconscious.—John Galsworthy

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It seems to me as if not only the form but the soul of man was made to walk erect and look upon the stars.—Bulwer

The Grey, Creeping Death

During the colonization of Asia and Africa the Europeans brought with them syphilis, to inspire later the unpleasant but not unjustified phrase: "Civilization means syphilisation."

The first wave of this new disease which swept across Europe in its virulent form was highly contagious and often fatal. . . . After a quarter of a century the disease changed its nature. It grew milder and its course was slower and more superficial. . . . Down the generations the disease lost more and more of its original virulence and malice. A small hard tumour, a swelling of the glands and after a few weeks a rash, no more serious than the measles—that was all. . . . As a result the fear of the disease abated. People ridiculed the precautionary measures and looked upon syphilis as a childhood disease which everyone had to suffer before he became a real man. The result was an overwhelming increase of syphilis in the seventeenth century, particularly in France. It was the so-called age of gallantry, and syphilis was called the "gallant sickness." It was "good form" to have it.

But sooner or later it took its toll. It ate away the victim's skin leaving putrid discoloured ulcers, particularly on the throat and the top of the head, making the hair fall out and leaving ugly scars.

The fashion of the age took this into account. It introduced the wig to disguise the baldness, created the jabot, which hid the ulcers on the neck under costly pleated lace, and made the wearing of gloves *de rigueur* to cover the hand sores with elegance and also to protect from possible infection by a handshake. The man of the Rococo age covered his whole body up to his chin and he had every reason to do so. Any blemishes on the face were covered with layers of powder and paint, and where this was of no avail with "beauty patches." The extravagant costume of the Rococo with its flowing periwigs and voluminous skirts was a white-wash to hide the syphilis.*

*H. S. Glasscheib, M.D.: The March of Medicine, 1964. Also see page 774.

Kidney Stone Surgery on the Frontier

Doctors took out kidney stones too. Dr. Hillary Ryan, Galveston, Texas, had a patient who had passed a squirrel tail into his urethra. A large stone had formed around the tail where it was lodged in the bladder. With three boys assisting, the doctor cut into the perineum with a pocket knife and removed a stone an inch in diameter. A second operation was necessary.

"We passed the director into the bladder and made an incision into the urethra," reported Dr. Ryan. "Passed a probe in, as before, and made the cut in the same direction, to the left of the rectum. As soon as the cut would permit the finger to pass into the bladder, the director was withdrawn, and the finger used. The opening was enlarged very slowly and carefully until we had extended it for about two inches and a half; we then, with some difficulty, drew out a stone one inch and a half thick by three and one-half inches long, and in it the squirrel's tail, of about five inches in length, one and one-half inches bent back on itself. It was in a good state of preservation and looked very much like salted meat." The patient recovered quickly.*

*Richard Dunlop, M.D.: Doctors of the American Frontier.

People who are much older than they look seldom have much intelligence.—G. C. Lichtenberg

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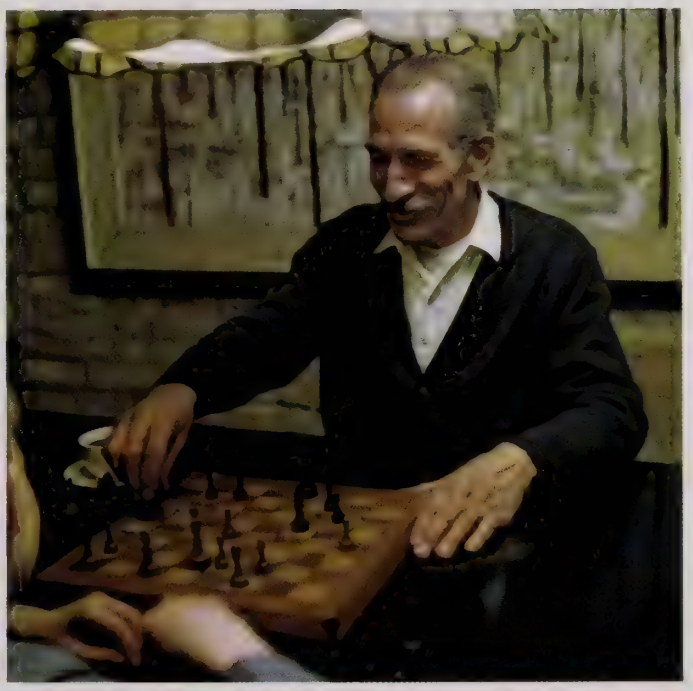
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1. Stern, S.B.: Med. Times, Oct. 1967
2. Reports on 1200 patients, data in files, Warren-Teed Pharmaceuticals, Inc. 1966

(See next page for prescribing information)

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Contraindications: Because of the danger of hypermagnesemia, MAGAN is contraindicated in cases involving advanced chronic renal insufficiency. MAGAN, as other salicylates, may counteract the effect of uricosuric agents, and should not be prescribed for patients on such drugs.

Warning: As with all salicylates, high dosages of MAGAN should be avoided entirely or administered with caution to patients with liver damage, preexisting hypoprothrombinemia, vitamin K deficiency, and before surgery.

Adverse Reactions and Precautions: The same precautions applicable to salicylate therapy in general should be followed in prescribing MAGAN. Appropriate precautions should be taken in prescribing MAGAN for persons known to be sensitive to salicylates. If reaction develops, drug should be discontinued. Dosages of anticoagulants should be reduced with the administration of high dosage levels of MAGAN. *Impaired Renal Function:* Appropriate precautions should be taken in administering MAGAN to patients with any impairment of renal function including discontinuing other drugs containing magnesium and monitoring serum magnesium levels particularly if dosage levels of MAGAN are high. *Salicylate Poisoning:* Symptoms of salicylism, resulting from high doses of MAGAN, can be expected to resemble closely in character and intensity those associated with aspirin poisoning. These range from dizziness, drowsiness and ringing in the ears to vertigo, convulsions, coma and hypokalemia. Salicylate poisoning can be treated by intravenous fluids with sodium bicarbonate or lactate and potassium supplementation. In very severe cases, hemodialysis may be necessary. Vitamin K, 5-20 mg. orally or slowly i.v., usually restores the prothrombin time to normal.

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The presentation of certificates and pins to Minnesota physicians who have engaged in the practice of medicine for 50 years has become an impressive highlight of each Annual Meeting. According to custom the presentations are made during the course of the Annual Banquet. Few who have witnessed these ceremonies soon forget the setting of such an occasion at which these colleagues with a half century of medical practice to their credit so alertly respond to the roll call.

The custom of honoring Minnesota physicians who have served their patients and communities for a half century was established in 1942. Forty-one physicians were honored at the first ceremony. This group also included those who had passed the 50-year mark prior to 1942.

To be eligible for this award a doctor must have spent the majority of his 50 years practicing medicine in Minnesota.

In 1968 seventeen doctors were added to the membership in this distinguished club.*

*See page 774: Senior Peers.



Richard E. Anderson, M.D.

Doctor Richard Anderson says he always had the ambition to be a doctor. After a business college course he became timekeeper in a large factory, and later a telegrapher. This gave him an opportunity to work nights, and to attend school days. Although he held many jobs while pursuing his education, he obtained high school, B.S. and M.D. degrees in eight years.

One of his most memorable days was when he delivered five babies in a day, all in farm homes, with no modern equipment and only a family to help.

His most interesting case was a patient who had a Staphylococcus septicemia. This occurred when the sulfa drugs were only on trial use to clinics. He was able to obtain some. After sulfa, 22 blood transfusions, 29 abscesses drained, and months in hospital, the patient recovered.

During his practice in Willmar, Doctor Anderson has conducted a busy general practice, performed many operations, and managed a private hospital for 15 years. And he has managed to do so while running a farm, participating in outdoor activities, and enjoying the company of his helpful and understanding wife.



Herbert H. Busher, M.D.

Doctor Herbert Busher was born in Sioux Falls, South Dakota, where his father was a minister. He was no ordinary student and at an early age declared to his father that he did not wish to enter the ministry but instead would like to become a doctor. After graduating from Concordia College, Dr. Busher went to the University of Minnesota where he graduated from Medical School in 1919. After a year of interning at the University Hospital, Dr. Busher completed a surgical residency and immediately thereafter opened offices in the Lowry Medical Arts Building. He died January 26, 1967.



Isabell L. Cameron, M.D.

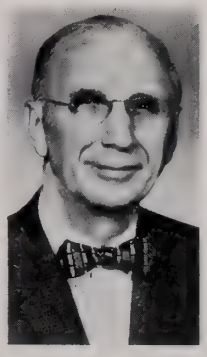
Doctor Isabell Cameron decided to become a doctor when she was ten. Why? Because her mother, a determined New Englander, informed her she was to become a physician. By 1918, she reached her goal and interned in Boston during the influenza pandemic of that year. After serving two years as an obstetrical resident, she entered general practice where her obstetrical experience served her well.

She remembers a bitterly cold winter night when she delivered a premature three-pound infant, warmed him in blankets, surrounded him with hot water bottles, and took him by car to St. Barnabas Hospital, where room rates were then one dollar a day. The child survived. Doctor Cameron says her role in practice was to treat, advise, and sympathize with those who needed her.



Woodard L. Colby, M.D.

Dr. Woodard Colby spends his leisure hours pursuing his hobbies of gardening, farming and bird watching. He is a graduate of the Minnesota University Medical School and has worked at Ancker, Lindsay, Gillette and the Shriners Hospitals. In addition to the University of Minnesota, Dr. Colby did graduate work at Harvard and Vienna. His specialty is pediatrics and he was an Assistant Clinical Professor of Pediatrics at the University of Minnesota. Dr. Colby is a former Vice President and President of the Ramsey County Medical Society.



Harold S. Diehl, M.D.

Doctor Harold Diehl decided to study medicine because he felt that the practice of medicine would be interesting, challenging and an opportunity to be of service to people. As his father was a minister his family background probably contributed to this feeling.

His most interesting and satisfying experience—although hardly a "case problem"—was the privilege of assisting in the development of a distinguished medical school at the University of Minnesota: one that is nationally and internationally respected for its undergraduate teaching, its graduate training programs and its contributions to medical research.

His major hobby has always been and still is work, interesting work, including writing. An important supplement to this is the time he spends at his summer cottage on Star Island, Cass Lake, Minnesota.

His favorite medical preaching, has probably been that physicians have an obligation not only to care for the sick but also to do everything possible to prevent disease, both personally and as community leaders.

Besides serving as dean of the medical school for 23 years at the University of Minnesota, Doctor Diehl became senior medical officer of the American Cancer Society. That society credits him with starting the events that led to the report by the Surgeon General of the U.S. Public Health Service on the dangers of smoking.



Frederick A. Figi, M.D.

Since retiring from the active staff of the Mayo Clinic about ten and a half years ago, Doctor Frederick Figi and his wife have traveled a good deal. But his chief interest now is woodworking, and he has converted his basement recreation room into a shop where he spends much of his time.

Here are excerpts from a Rochester Post-Bulletin article—"Retired Plastic Surgeon is Wood Hobbyist."

"Dr. Figi has always been interested in highly polished hard woods but not until retirement did he have ample time to work with them.

"He has had woods shipped back from his travels to West and South Africa, South America and Mexico, as well as stops on the couple's world tour in 1957-58. A number of former patients have sent him generous portions of exotic woods from remote foreign areas.

"In 1961 Dr. Figi was featured in the Post-Bulletin for his cane collection. He now has more than 300 canes and walking sticks of various shapes and uses collected over a period of 37 years."

While woodworking is an all-absorbing hobby for the retired physician, Doctor Figi assures us that it falls far short of the gratification and sense of accomplishment afforded by the practice of medicine.



Albert Fritsche, M.D.

Doctor Albert Fritsche took up medicine because it was in his family. His father, the late Doctor L. A. Fritsche, sent four sons through medical school. The younger Doctor Fritsche started practice in New Ulm in 1919, and what sticks in his mind are the cases like the following which he had in his first two years of practice.

One dark night he entered a strange farmhouse to deliver a child. When he entered the room, a hysterical pregnant woman stood in the bed. She flung herself at his feet. While relatives restrained her, he gave chloroform and managed to deliver a child that was in a breech position.

Later he and his father consulted on the case of a 58-year-old woman who experienced abdominal pain one month before and then ran a fever. When she became short of breath, they detected dullness in the chest. They resected a rib, and entered a pus cavity that contained 12 gallstones.

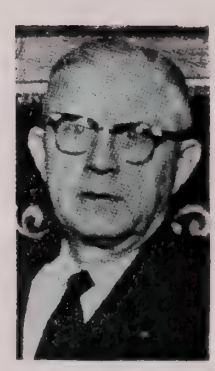
Doctor Fritsche handled these and similar cases without the help of laboratory and x-ray facilities.



Joseph N. Gehlen, M.D.

Doctor Joseph Gehlen obtained his medical education at Creighton University in Omaha, Nebraska. Born in Lemars, Iowa, Dr. Gehlen came to Minneapolis in 1921 to accept a position with the Minnesota State Board of Health. He is presently associated with Dr. C. N. Hensel in the practice of internal medicine in the Central Medical Building in St. Paul.

Dr. Gehlen was chief of the tuberculosis service at Anker Hospital in St. Paul for many years.



Silas W. Giere, M.D.

The earliest medical experience of Dr. Silas Giere's life occurred at age 3, when his father took him by long train ride from his country parish to St. Paul. There a doctor and nurse gave him sweet-smelling perfume (chloroform) and comforting words, then removed his tonsils. This experience made him feel "that's for me" and in the ensuing years confirmed his resolution to become a doctor.

The experience he remembers best was one night when a snowstorm raged. At 10:30 p.m. a phone call precipitated "the doctor" on a drive behind horses, to a maternity case across the prairie, cutting fences, rolling out of the sleigh several times, stopping in a farmyard to repair a breakdown of the sleigh, arriving at 6:00 a.m., delivering the baby, and returning home at noon. This was one of many similar experiences.

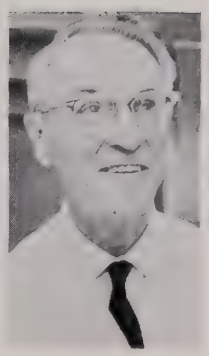
His outstanding day occurred in Lower Antilles. There the whole city turned out at the small airport in early days when his cable for reservations was confused by local officials, and the local populace came to the airport to meet Greer (Garson).

His most mysterious case was a thought-to-be drunk upon whom he performed a successful tracheotomy with a dirty knife, as he lay on the floor, cyanotic. Apparent cause? A bee sting while haying.

Since leaving the Department of Pathology at the University of Minnesota, Dr. Anderson C. Hilding has been in Duluth carrying on both the practice of Eye, Ear, Nose and Throat and investigative work, the latter occupying his full time. Through these years, interspersed with this work, has been an academic year in Vienna, two years at the Mayo Clinic, a year as Visiting Research Professor in Otolaryngology at Columbia, and a winter session in India doing eye surgery at a Mission Station.

One of his outstanding experiences was the thrill of presenting a research paper with his son (Associate Professor of Ear, Nose and Throat at Yale) in which both spoke before the 1966 American Laryngological Association Meeting in Puerto Rico.

On the lighter side, one of his most memorable surgical experiences occurred in the Emergency Room when a group of plump, middle-aged inebriated, overly-dressed women presented themselves and one of their number claimed to have swallowed a candle stick. She indicated the general region of the larynx and said that at a party she had taken a bite of birthday cake. He began to anesthetize her throat with cocaine solution, meanwhile trying to dodge the resulting rivers of alcohol and stomach contents. He was using a small swab on a long, curved, wire applicator in the laryngeal pharynx, when it seemed that the patient grasped it with her pharyngeal muscles and there was some resistance in pulling it out again. To his amazement, when he laid the swab on the table, something had been added—the tip of the swab had entered the opening of a coiled wire candle stick, such as were found in the candy flower candle-holders used to decorate birthday cakes of that era. The intern, leaning over his shoulder, commented, "Gosh, doctor, you did that neatly." The patient, when she saw it, stood up and raised her fists as high as she could reach, proclaiming, "..... ....., ... didn't I tell you girls I swallowed a candle stick!"



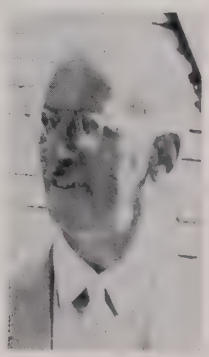
Anderson C. Hilding, M.D.

Instead of talking of his life since graduation, Dr. Charles Lick prefers to report this case: Forty-four years ago a young woman came to his office because of a tumor of the distal end of her right radius. There had been a minor injury a few weeks before. After the injury, a small nodule appeared and grew rapidly. Dr. Lick recommended amputation on the basis of the biopsy which Dr. A. T. Bell interpreted as giant cell sarcoma.

The husband refused an amputation and accordingly only the distal end of the radius was removed. The wound healed and some time later a leather support was used to hold the hand in position.

In 1968 the patient returned to the office of Dr. Lick still in good health with no recurrence of the tumor. A review of the slide from 1924 showed a giant cell tumor—a tumor not generally recognized as benign until Jaffe's work in the 1940's.

Dr. Lick is happy to report that this was one instance in which the husband's advice for this radical treatment proved to be better than his own.



Charles L. Lick, M.D.



Thomas A. Lowe, M.D.

As a farm boy, Doctor Thomas Lowe decided early to be a doctor He worked hard, finished high school in three years with honors and then worked through seven years at the University of Minnesota. During those years, he was in turn a butcher, livery man, drayman, cream hauler, elevator tender, shoe shiner, paper seller, junk dealer, house-to-house salesman, farm hand, dishwasher, furnace keeper and waiter on tables.

He left medical school and went overseas in World War I with the Mayo Base 26. There he assisted surgeons in a 20,000 bed hospital. Once he took care of 65 fractured legs at one time. When the war was over, he volunteered for rehabilitation work in Serbia and was in charge of a hundred-bed hospital. The government decorated him twice and recommended him as Chief Surgeon of a 300-bed hospital with the rank of Major. He declined, came home, and took refresher courses before practice.

He did general practice but preferred surgery. He was formerly in group practice with the late Dr. Earl Lowe and is now in practice with his nephew Dr. Alex Lowe, at the same location for 42 of his 50 years.

Dr. Lowe is a fellow of the International College of Surgeons and a fellow of the Industrial College of Surgeons, a member of the American Medical Association, Minnesota State Medical Association and the Ramsey County Medical Society.

He gets up early, sees his hospital patients early, and walks a mile before opening the office. He had many hobbies early in life but has bypassed them for work. He was lucky in marriage, has one daughter, a son-in-law and three grandchildren. He has good health, a strong constitution and a busy practice people kindly give him.



Donald McCarthy, M.D.

Doctor Donald McCarthy divides his life in medicine into three periods. The first began in 1919 when he was discharged from active duty with the Navy. He started to practice internal medicine in Minneapolis as an assistant to Dr. J. G. Cross for three years. Then he entered his own practice, sharing office space with Dr. Henry. This first period ended in 1941, when he again entered the service, this time as a Junior Medical Officer at the Naval Hospital, Great Lakes, Illinois. He served successively as Senior Medical Officer of the Minneapolis Recruiting Station, Chief of Medicine on the U.S. Hospital Ship "Relief" in the Atlantic and Pacific, as Chief of Medicine and Executive Officer of the Naval Hospital at Great Lakes, and as Senior Officer at the Naval Operating Base at Midway Island.

The last period—the Administrative Period—commenced in 1946 when he entered the Veterans Hospital system as a Deputy Area Medical Director. He supervised veterans' hospitals and clinics in the North Central States until he retired in 1965. When that event occurred, he accepted an administrative position at the Minnesota Department of Health, a position he still occupies on a part-time basis.



Christian L. Roholt, M.D.

Doctor Christian Roholt of McIntosh, Minnesota, tells that he inherited his urge to care for the sick from his mother and father. After he graduated from the University, he started to practice and eventually had his own hospital in Waverly, Minnesota. The two cases that he remembers most vividly were both women. One was brought to his office nearly dead from uterine bleeding. Because of her desperate condition, he gave intravenous saline, and then removed her uterus: she survived. The other patient was a newlywed who told him she would die when she delivered her first child. To reassure her, he spent the night with her while she was in labor. After an easy delivery, she began to fail rapidly and died at 5:00 p.m. the same day. Besides these two cases, Dr. Roholt recalls most vividly the day he examined and cared for 64 patients.



Lloyd H. Rutledge, M.D.

Doctor Lloyd Rutledge left high school, went to Kansas City, and afterward into the business world. After eight months on a salary of $12.00 per week, he quit and enrolled as a premedical student at the University of Missouri.

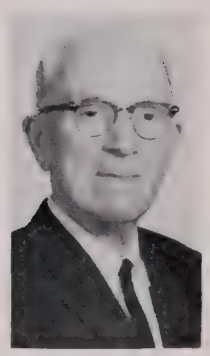
Why medicine? First, his father was a country doctor in a small town; second, from his view from a small room in a Kansas City rooming house, the business world looked too tough.

He transferred to the Minnesota University for two reasons: first, a Fellowship in anatomy under Dr. Jackson furnished $550.00 a year to help pay expenses; second, the Mayo Clinic was affiliated with the University of Minnesota.

After medical school, he had a chance to practice at Detroit Lakes for the summer of 1919 as a seasonal job while he waited for a Fellowship to open at the Mayo Clinic. But after summer nights, canoe rides, a girl named Nancy, the golf course and the walleyed pike, he began to like northern Minnesota. Then came the wild rice and the duck shooting, not hunting but shooting, and he forgot about the University and Minneapolis. The town needed a new doctor and a hospital. He drove a car, a team and sled, shovelled carloads of snow, delivered babies at 5:00 A.M. in the country, shot 10 ducks and got back to the office by 10:00 A.M.

His most interesting case was in the 1920's when he ran into a typhoid-like case, but the woman had a little red streak on her hand from cleaning a young cottontail rabbit. After three weeks—no diagnosis. Further requests for blood were refused. A consultant, Dr. W. H. Long of Fargo, suggested rabbit fever. A few minutes after she died, he drew the blood, and the first case of tularemia in Minnesota was reported.

But I have not given up the ducks and the golf—not yet, thank God!



Virgil J. Schwartz, M.D.

Doctor Virgil Schwartz, born in Romania in 1894, came to Minneapolis at six and graduated from the University of Minnesota Medical School in 1919. He trained at the University and General Hospital in ophthalmology and otolaryngology. Then in 1923, after spending about a year abroad in the field of bronchoesophagology, he began to practice in Minneapolis. During his 40 years of practice, he wrote numerous articles, and had "through sheer luck, the opportunity to report five or six medical entities which had not previously appeared in literature."

Doctor Schwartz' family particularly enriched his life. During his training at Minneapolis General Hospital he met and later married Mary L. Dean. They had one daughter and two grandchildren. Doctor Schwartz and his wife shared interests in music, literature, drama, opera, current affairs, travel, and sports.



James F. Weir, M.D.

Dr. James F. Weir, a Mayo Clinic staff member for 33 years, head of a section of medicine, and chairman of four sections of medicine, was born of farm parents in Byron, Ontario, in 1893. He graduated in medicine from Western University in London, Ontario, in 1918, and was an officer in the Royal Canadian Army Medical Corps in England in 1918 and 1919. He interned at the University of Minnesota Hospitals for eight months in 1919 and 1920.

Dr. Weir came to Rochester, Minnesota, in 1920 as a fellow in medicine in the Mayo Graduate School of Medicine; he was appointed to the staff of the Mayo Clinic in 1925. He became an instructor in medicine in the Mayo Graduate School of Medicine in 1925 and was advanced to assistant professor in 1933 and to associate professor in 1944.

A gastroenterologist, he helped develop intravenous therapy for the dehydration and hypochloremia of pyloric obstruction, and he showed how vitamin K could be used to control hemorrhage in the jaundiced patient. His acumen and mastery of physical diagnosis caused him to be known as the "physician's physician."

"I have no clear idea of why I entered medicine," he has said, "but farming did not interest me. Educational facilities were available in the area in which I grew up, and some acquaintances there had taken up medicine. I suppose I did so because they did.

"Success in the practice of medicine involves many things. Of these, the history the patient gives is the most important. Take your time, listen carefully. Thus I was trained, thus I practiced, thus I preached."

He reports that the outstanding event in his career "was the occasion when I was elected president of the staff of the Mayo Clinic for 1949, an honor which was wholly unexpected and was sincerely appreciated as an expression of the esteem of my colleagues."

He was married to Miss Edna E. Enke of Rochester in 1921; he and Mrs. Weir have two daughters. He devotes his spare time to studies on the genealogy of his and Mrs. Weir's families, and to cabinet work at his home in Rochester.

The Viewing Box

An Unusual Case of Bilateral Obstructive Uropathy

The two x-rays shown here are from intravenous pyelogram studies taken two months apart on a six-year-old male child. The first study appears on the left. It was obtained three months after the patient was hospitalized for a neck mass diagnosed as reticulum cell sarcoma. He was treated surgically, followed by radiation therapy, and then placed on intravenous cyclophosphamide.* Following discharge, the patient was continued on the drug orally. He did well until he experienced the sudden onset of hematuria, dysuria, urgency and frequency. A urine culture was sterile and the first intravenous pyelogram (Figure 1) showed bilateral hydronephrosis and ureteral dilatation down to the bladder, which was noted to be markedly contracted and irregular in contour. It was felt that the upper tract changes may well be secondary to bladder spasm. Two months later, a repeat intravenous pyelogram (Figure 2) was performed which showed not only normal upper urinary tracts but a normal bladder outline also.

What is your diagnosis? (See next page.)

*Cytoxan (Mead Johnson).



Figure 1



Figure 2

Diagnosis—Cyclophosphamide Hemorrhagic Cystitis.

The above condition was considered a strong possibility when this patient developed his urinary tract symptomatology; so the drug was discontinued and the patient maintained on forced hydration. The remission was spontaneous and the recovery complete as evidenced by the second intravenous pyelogram film (Figure 2).

Cystitis is a relatively common occurrence in patients who are undergoing cyclophosphamide therapy, and it may develop after either intravenous or oral administration of the drug. Usually with intravenous administration, the symptomatology occurs in 24 to 48 hours, but it may take a month or more before the condition is manifest when the drug is taken orally. The condition is characterized by dysuria, urgency, frequency and hematuria, and the urine culture is characteristically sterile.

Cystoscopy reveals a hyperemic, edematous bladder with many areas of hemorrhage but, after withdrawal of the drug, the symptoms usually subside in four to five days, with complete resolution by two months.

Prolonged use of the drug in the face of the hemorrhagic cystitis may produce chronic fibrosing cystitis with exsanguinating hemorrhage.

Patients receiving Cytoxan* should therefore be followed carefully for symptoms of bladder irritation. In most cases discontinuation of the drug and forced hydration will be sufficient for controlling the condition.

Robert D. Bugby, M.D.*
Edina, Minnesota

*Department of Radiology, Fairview-Southdale Hospital.

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The Progress Notes of Hippocrates

In Larissa, a man, who was bald, suddenly was seized with pain in the right thigh; none of the things which were administered did him any good. On the first day, fever acute, of the ardent type, not agitated, but the pains persisted. On the second, the pains in the thigh abated, but the fever increased; somewhat tossed about; did not sleep; extremities cold; passed a large quantity of urine, not of good character. On the third, the pain in the thigh ceased; derangement of the intellect, confusion, and much tossing about. On the fourth, about noon, he died. An acute disease.—Hippocrates

Editor's Note: Diagnosis and Treatment: Arterial Embolus.
Your diagnosis and treatment?———————

Medical Seminar

The Platelet in Hemostasis

Presented as a Seminar

Sponsored by

The Faculty of the Mayo Graduate School of Medicine

WRIGHTS' HYPOTHESIS of the origin of blood platelets as fragmented portions from the cytoplasm of the megakaryocytes of the bone marrow is generally accepted. These platelets or thrombocytes are small non-nucleated structures measuring 2 to 4 μ in diameter and arise from the adult megakaryocytes, the largest of all normal marrow cells, measuring 50 to 150 μ in diameter. By volume measurements it has been estimated that 4,000 platelets are produced from a single megakaryocyte.[2]

Over the past several years, advances in platelet physiology and biochemistry have shown platelets to be viable cell fragments requiring and producing energy for their major function in hemostasis. It is their activity and unique metabolism in normal spontaneous hemostasis that will be discussed.

Morphology

When examined in the capillaries, platelets appear as small, round, or oval disks. In vitro they may maintain this appearance in a suitable ionic environment and in the presence of colloids, but usually become spherical with numerous spiny processes protruding from their surfaces. They may then assume triangular, quadrangular, crescent, dumbbell, or other bizarre and irregular forms. Pseudopodia or dentritic processes are numerous if the smear is made on a nonwettable surface, but are not seen when the smear is made directly on a glass slide. When observed by time-lapse cinematography, the platelets as they leave the vessels can be seen to throw out filamentous dendritic processes which are wide at their bases. As one of these projections touches a glass slide, it sticks to the surface and enlarges; other dendrites also become fixed. The cell then becomes completely adherent to the slide and is usually round with a central granular area, or granulomere, and a clear surrounding area or hyalomere. These platelets are often referred to as spread or resting forms.[3]

Ultrastructure

Details of platelet ultrastructure after osmic acid fixation and ultrathin sectioning, as seen with the electron microscope, have been observed. The cell membrane is 5 to 8 mμ thick; fifty to 100 oval homogeneous granules 0.15 to 0.25 μ in diameter and encompassed by a thin membrane have been described. Mitochondria with few cristae are present, similar in size to that of the granules. The hyaloplasm contains numerous tubules and microvesicles, as well as siderosomes, the ferritin-containing structures.[4,5]

The major biologic activities of blood platelets will be discussed in the following sections.

Adhesiveness and Aggregation

If an arteriole or venule is transected under direct microscopic observation, adhesion of platelets to the edges of the cut vessel is seen to occur within seconds. The specific force that draws the platelets to the denuded vascular surface is not known. The phenomenon has

been called platelet "stickiness." It has long been known that platelets in certain instances adhere to foreign organic particles such as yeast, some microbes, and on organic surfaces such as glass barium sulfate and alumina.[6]

Electrostatic Potential

Recent observations suggest that an electrostatic potential may be a factor, since it has been shown by electrophoresis that platelets carry a net negative charge. Sawyer and Pate,[7] by applying a small electrical current to a blood vessel wall, were able to initiate the formation of a platelet thrombus at the site of a positive but not a negative current. Although adhesion on the basis of a difference in electrostatic charge is an attractive hypothesis, it has some defects. Blood cells other than platelets normally bear negative charges too, but do not adhere to damaged blood vessels and cannot be interchanged for platelets. Some have maintained that the difference between other blood cells and platelets may be due to differences in ionic groups in the cell surface[8] or to differences in cell size,[9] thus adhesion due to electrostatic force is still a possible explanation. Recently it was shown that the collagen connective tissue to which platelets adhere has an electrophoretic mobility* similar to that of platelets.[10]

Selective Affinity

From these studies, therefore, adhesion does not seem to be a simple matter of unlike surface attraction. It became apparent that platelets adhered not to injured cells, but rather to intercellular junctions and to areas denuded of endothelial cells.[11] More recent studies have shown that there is a selective affinity of connective tissue for platelets. Using ground fragments of aorta, Bounameaux[12] noted that there was no adhesion of platelets to endothelial cells, but observed their immediate agglutination to fibers apparently of vascular connective tissue origin. Others noted that when animal mesentery was traumatized and then subjected to platelet-rich plasma, aggregation of platelets occurred only in the traumatized tissue and to the elastic and collagen fibers.[10,13] Zucker and Borrelli[14] demonstrated that collagen was the tissue component to which the platelets adhered; and they confirmed this observation by showing that collagenase destroyed the activity of the connective tissue suspension. These observations have been confirmed by electron microscopic studies, which show that in platelet plugs occurring at the site of a transected arteriole the platelets adhere to the perivascular connective tissue and not to the endothelium.[15] It appears then that platelets do not normally adhere to endothelium and intercellular substance; but that platelet adhesion occurs only when the endothelial cells are traumatized and underlying collagen connective tissue is uncovered.

Platelet Cohesiveness

Subsequent reactions involve platelet cohesiveness. Under normal conditions, when platelets have adhered to collagen fibers, new platelets soon aggregate to these fixed platelets and to each other, forming platelet clumps. Agglutination of platelets in vitro has been induced by various means, and at times spontaneous clumping of platelets has made study difficult. Cooling increases the cohesive property of platelets, as do certain heavy metals.[16] Clumping occurs in the presence of heparin. Platelets are also aggregated by antigen-antibody complexes, polystyrene particles, latex particles, bacteria, viruses, uric acid crystals, and many other agents including fibrinogen preparations. Glynn and co-workers[17] showed that when platelets in citrated platelet-rich plasma were exposed to particulate matter such as latex particles, the platelets phagocytosed the particles.

There are, however, two agents which physiologically seem to act in platelet cohesion. The first of these is thrombin, which has long been known to clump platelets rapidly, with an apparent loss of platelet integrity as seen by light microscopy.

The effect of thrombin on platelets has been called *viscous metamorphosis.*** Viscous metamorphosis is initiated by thrombin probably produced by the extrinsic or tissue thromboplastin system. The thrombin, acting with fibrinogen adsorbed to the platelet's surface, as well as with that present in the surrounding plasma in the presence of calcium and magnesium, contributes to this process. During this

*See Test Your Word Score Page 797.

**The term "viscous metamorphosis" was originally used by Eberth and Schimmelbusch[18] in 1886 to describe changes in single platelets. The term is used to refer to such a wide variety of clotting processes that it has almost lost its usefulness. In present-day studies the terms platelet "aggregation," "agglutination," "clumping," "cohesion," and "fusion" tend to be used.

viscous metamorphosis there occur a degranulation of the platelets and the release of serotonin, biogenic amines[19] (histamine, catecholamines), adenosine diphosphate, inorganic phosphate, platelet factor 3, free amino acids, potassium, acid phosphatase, and other constituents.[20] Although platelets appear to be fused into an amorphous mass during viscous metamorphosis, the electron microscopic studies by Kjaerheim and Hovig[15] showed that the platelet membranes are preserved without apparent breakdown of gross platelet structure. The viscous change previously observed by light microscopy therefore represents tight adherence of platelets without actual fusion. During viscous metamorphosis additional thrombin is generated via the intrinsic or plasma thromboplastin system, and growth of the platelet aggregate ensues. Viscous metamorphosis, once initiated, thus ensures its own propagation.

The second agent causing platelet cohesion was discovered in erythrocytes in 1960[21] and identified as adenosine diphosphate.[22] It had previously been known that platelets contained high concentrations of adenosine triphosphate, which disappeared with platelet aggregation. Since adenosine diphosphate is the first breakdown product of adenosine triphosphate, these observations suggested that the increase in adhesiveness brought about by adenosine diphosphate might underlie the physiologic mechanism responsible for the formation of hemostatic plugs. This hypothesis is now supported by considerable evidence.

The Factor of Aggregation

Born[23] has made the following observations regarding aggregation by adenosine diphosphate: (1) It is found in all animal species in which it has been looked for. (2) It is effective, rapid, and highly specific. (3) It does not involve dephosphorylation of adenosine diphosphate. (4) It requires calcium and at least one plasma protein, almost certainly fibrinogen. (5) It is reversible. (6) It is involved in aggregation caused by other agents including thrombin, fatty acids, catecholamines, and collagen.

Born[23] has further emphasized that aggregation by adenosine diphosphate can be inhibited in the following ways: (1) by deficiency or inactivation of a component of the platelets, (2) by deficiency or inactivation of the plasma protein, (3) by lack or excess of ionic calcium, (4) by elimination of adenosine diphosphate by the action of enzymes, and (5) by certain substances related to adenosine diphosphate, specifically its breakdown products, adenosine monophosphate and adenosine.

The mechanism of adenosine diphosphate aggregation is not known. *One hypothesis suggests* that a complex composed of adenosine diphosphate, calcium, and a plasma protein, perhaps the von Willebrand factor, makes bridges connecting adjacent platelets.[24] *A second hypothesis is* suggested by Born, who feels that bombardment by adenosine diphosphate molecules may cause a configurational change in a protein on the platelet surface, and that this change is required for the formation of disulfide bonds between platelets and molecules of fibrinogen. Evidence in favor of Born's hypothesis is that (1) in the presence of adenosine diphosphate the platelets swell before they aggregate, (2) there is minimal or no binding of adenosine diphosphate to the platelets, and (3) aggregation but not swelling is inhibited by substances that block sulfhydryl groups and by others, such as dimercaprol and dithiothreitol, which tend to preserve sulfhydryl groups intact or break disulfide bonds.[23] The aggregation of platelets in vitro by adenosine diphosphate is inhibited by adenosine, and more strongly by 2-chloroadenosine.[25] It has been proposed that an enzyme system in the platelets and plasma constantly reestablishes adenosine monophosphate-adenosine diphosphate ratios capable of inhibiting platelet aggregation, thus preventing a self-extending process.

Salzman[26] has proposed yet a *third hypothesis for the mechanism* of platelet aggregation. He has noted that the addition of adenosine diphosphate to platelet-rich plasma leads to breakdown of the adenosine diphosphate through stepwise dephosphorylation to adenosine, which then is incorporated by the platelet. He theorizes that the presence of adenosine diphosphate in the platelet environment inhibits the splitting of adenosine triphosphate to adenosine diphosphate by platelet membrane

ATPase. Salzman suggests that the platelet membrane ATPase normally keeps the platelet in an unsticky state and maintains the cell size and shape. He feels that adenosine diphosphate inhibits the platelet membrane adenosine triphosphatase, resulting in platelet stickiness by exposing adhesive sites and permitting platelet aggregation to occur through intermediate secondary bridges containing calcium, fibrinogen, or other proteins. Spaet and colleagues[27] object to this hypothesis on the grounds that it fails to account for the extremely minute concentrations of adenosine diphosphate that are effective in aggregating platelets, for such amounts do not inhibit adenosine triphosphatase-adenosine diphosphate conversion. They feel that the concentration of adenosine diphosphate that actually reaches platelets in platelet-rich plasma is probably significantly less, since the plasma adenosine diphosphatase is capable of effecting considerable adenosine diphosphate breakdown en route. From the foregoing discussion it is obvious that the mechanism of platelet aggregation is unsettled.

As mentioned previously, serotonin (5-hydroxytryptamine) is released from the platelets during the process of viscous metamorphosis and may assist further aggregation, as well as produce local vasoconstriction. In support of this concept is the observation that parenteral serotonin reduced the blood loss of cut rat tails without affecting the bleeding time.[28] There remains some conflict in the literature, however. Studies by Salzman[29] in rabbits treated with reserpine to deplete serotonin showed no prolongation of the bleeding time. When similarly treated rabbits were also given heparin, the bleeding time was prolonged. These observations are in keeping with the concept of the hemostatic triad in which vasoconstriction, platelet aggregation, and blood coagulation act conjointly in producing hemostasis. A combined defect of these activities would therefore be necessary to explain the prolonged bleeding. Serotonin alone does not seem crucial in human hemostasis, since serotonin-depleted patients rarely have a hemorrhagic disorder.

The Platelet and Blood Coagulation

It is known that a platelet plug can temporarily arrest bleeding. Hemostasis, however, is not complete until the platelet plug is reinforced by a fibrin clot. To contribute to their function in hemostasis, blood platelets contain materials active in blood coagulation. Whether the platelets produce these factors, or whether they merely act as sponges acquiring the factors from the surrounding plasma, has not been determined. Two types of platelet clotting factors have been distinguished according to their localization and origin:[30] those that are adsorbed from the plasma onto the platelet surface and those that are a part of the platelet structure.

Platelet Factor 1

The following plasma clotting factors are those felt to be adsorbed to the platelet: fibrinogin (I), II, V, VII, VIII, IX, X, XI, XII, and XIII. Elution studies have shown a variability in the tightness of adhesion of these various factors.[30] Of note is the fact that platelet factor 1 is probably adsorbed plasma factor V. There remain three platelet factors and probably a fraction of the platelet fibrinogen. These are felt to be "true platelet factors" and a part of the platelet structure.

Platelet Factor 2

Platelet factor 2 accelerates the conversion of fibrinogen to fibrin by thrombin and has been called "thrombin accelerator" or "fibrinoplastic factor."

Platelet Factor 3

Platelet factor 3 is a lipoprotein in which the active lipid components appear mainly to be phosphatidyl serines and phosphatidyl ethanolamines. Deutsch and Lechner[30] state that the lipid portion can easily be separated from the protein part by extraction with lipid solvents, and they note that these lipids can substitute for the whole platelet factor 3 in almost all coagulation tests. Both platelet granules and surface membrane contain the lipoprotein.[19] In intact platelets the lipoprotein is not available for clotting. However, it is theorized that during viscous metamorphosis there is a reorientation of the platelet surface lipids, as well as a release of granules. It is further speculated that factor 3, thus made available, reacts to form intrinsic prothrombin activator which is important for the induction of the first phase

of clotting at the site of the platelet plug.[31] In addition, Spaet[10] postulates that the reoriented platelet surface lipids possibly provide a surface capable of initiating clotting by activating Hageman factor (factor XII).

Platelet Factor 4

Platelet factor 4 is a protein or high molecular weight polypeptide that is believed to be a component of the hyalomere. Its function of directly neutralizing heparin was initially suspected from the clinical observation that patients with a reduced number of platelets have an increased sensitivity to heparin. Recently it has also been shown to interfere with the action of fibrinogen breakdown products.[32]

Intrinsic Platelet Fibrinogen

Intrinsic platelet fibrinogen was suspected when it was shown that platelet extracts clotted if thrombin was added. Studies in the last two years by Castaldi and Caen[33] have shown that adsorbed fibrinogen could be removed by intensive washings. If the platelets were then disrupted, the platelet fibrinogen was again found in the extracts.

The Platelet and Clot Retraction

Roskam[6] in 1961 reported that, on direct microscopic observation of in-vivo hemostasis, new platelets were constantly being added while others were constantly being dislodged by the stream of flowing blood from the initial friable platelet aggregation.

Platelet Retraction

As this initially loose platelet aggregate enlarges, it is converted into a compact hemostatic plug by the platelet's ability to retract. This may occur within a few minutes. The ability to shrink to a solidly fused mass was found to be due to a contractile protein in platelets called "thrombosthenin." Thrombosthenin constitutes approximately 15% of the total protein of platelets and is an actomyosin similar, in some respects, to muscle actomyosin. Both muscle and platelet contractile proteins contract or superprecipitate at low ionic strength in the presence of adenosine triphosphate and magnesium ions. Both also have adenosine triphosphatase activity, splitting a phosphate group from adenosine triphosphate to form adenosine diphosphate. Like muscle actomyosin, the adenosine triphosphatase activity of thrombosthenin is activated by magnesium ions and, to an even greater extent, by calcium ions. Muscle actomyosin differs from thrombosthenin both in its immunologic properties and in the dynamics of its adenosine triphosphatase activity.

Clot Retraction

Clot retraction was found to be inversely proportional to the fibrinogen content of the red cell mass, since the more red cells and fibrin in the clot, the less it can contract. It has been shown that clot retraction is an energy-consuming reaction requiring intermediate glucose metabolism and producing lactic acid. What initiates the clot retraction is not known, but Spaet[10] suggests that it may be triggered by the action of thrombin. He showed considerable increased compactness of a platelet aggregate after exposure to thrombin for one minute. Platelet cohesion after this type of exposure to thrombin remained and resisted washing after 30 minutes of incubation. He noted considerable dispersion in a similar platelet aggregate without thrombin exposure; after a gentle saline wash only adhesion remained.

Platelets and Vascular Integrity

It is felt by many observers that platelets participate in some way in the preservation of vascular integrity. Increased vascular fragility has long been recognized in cases of prolonged and severe thrombocytopenia. Kramár[34] by using various methods of platelet suppression, was able to show a striking parallel between decreased platelet count and decreased capillary resistance, and he concluded that the vascular bleeding tendency resulted from a specific association of the two factors: low capillary resistance and platelet deficiency. Witte[35] demonstrated that in experimental thrombocytopenia there is increased vascular permeability to fluorescein-labeled proteins. Viable platelets were labeled with ^{35}S and injected into thrombocytopenic rats[36] and into normal pigs;[37] and later the ^{35}S label could be demonstrated in the blood vessel walls. Certain observations indicate that it does not require the presence of viable platelets to improve vascular integrity. Patients with thrombocytopenic purpura have shown improved vascular integrity when given

lyophilized platelet material. Klein and colleagues[38] noted that this effect occurred without elevation of the platelet count. They speculate that hemostasis and vascular integrity may not necessarily depend on morphologically intact, circulating platelets, but may be related to separable components. Others have failed to demonstrate an improvement in hemostasis unless the infused platelets were viable.[39] What the specific components are and how they participate in maintaining vascular integrity remain to be demonstrated.

Hemostasis in Larger Vessels

The foregoing discussion was concerned mainly with the platelets' ability to effect hemostasis by forming a platelet plug in small vessels. Defects in larger vessels are also influenced by platelet action. The initial platelet aggregate or white thrombus initially slows blood flow and further acts as a nidus around which fibrin is deposited. The fibrin, which is laid down as a network of dense strands, then adds to the local trapping of blood cells with the establishment of a red thrombus, thus sealing the defect in the larger vessel. Platelets therefore appear to participate in hemostasis no matter what the caliber of the vessel.

Summary

Blood platelets have been discussed as viable cell fragments with a dynamic metabolism whose major function appears to be in hemostasis. Major biologic activities of platelets are those concerned with adhesiveness and aggregation, blood coagulation, clot retraction, and vascular integrity.

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This paper was prepared under the supervision of members of the faculty of the Mayo Graduate School of Medicine.

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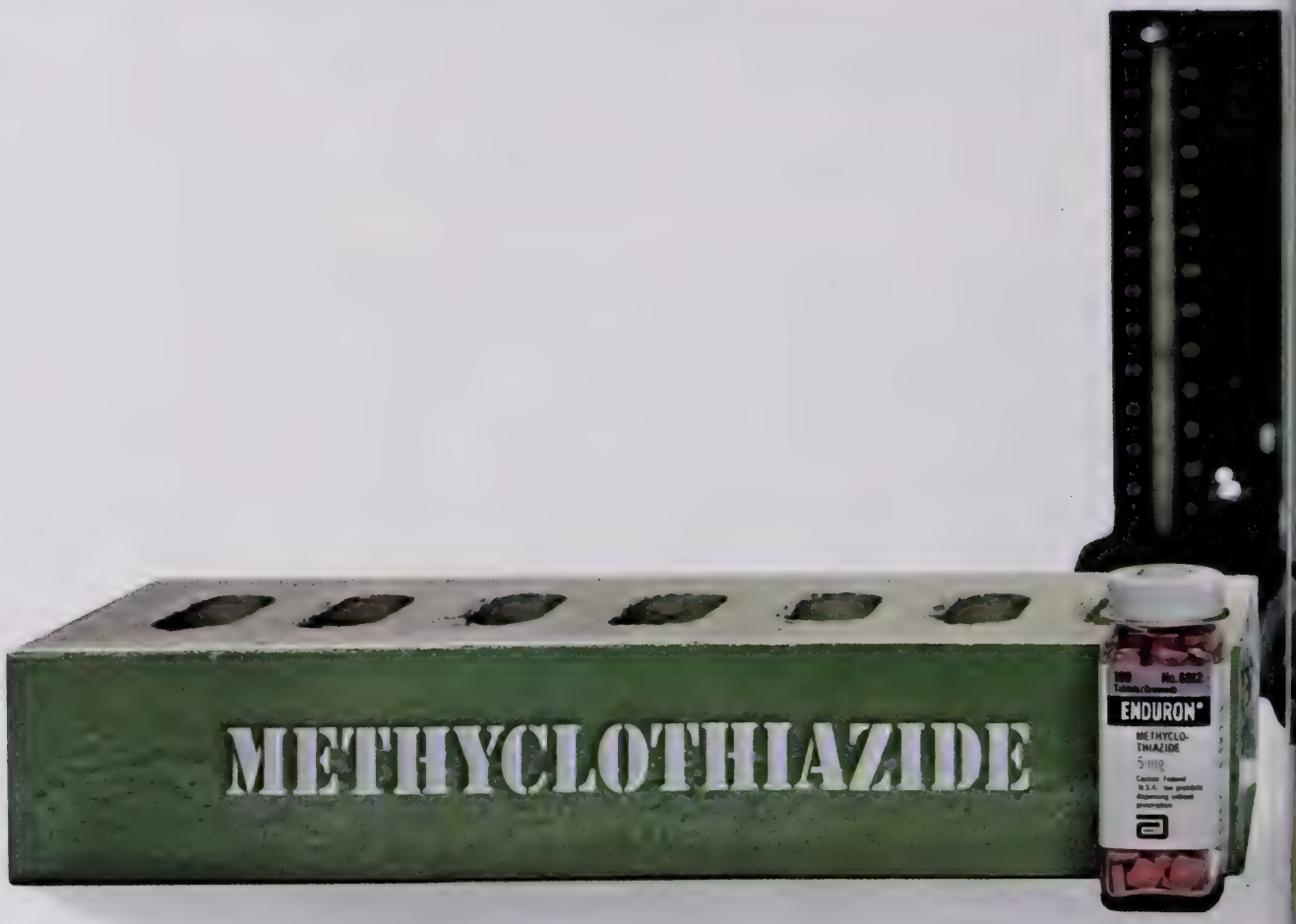
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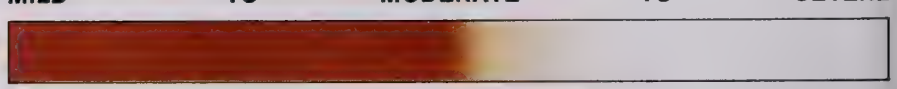
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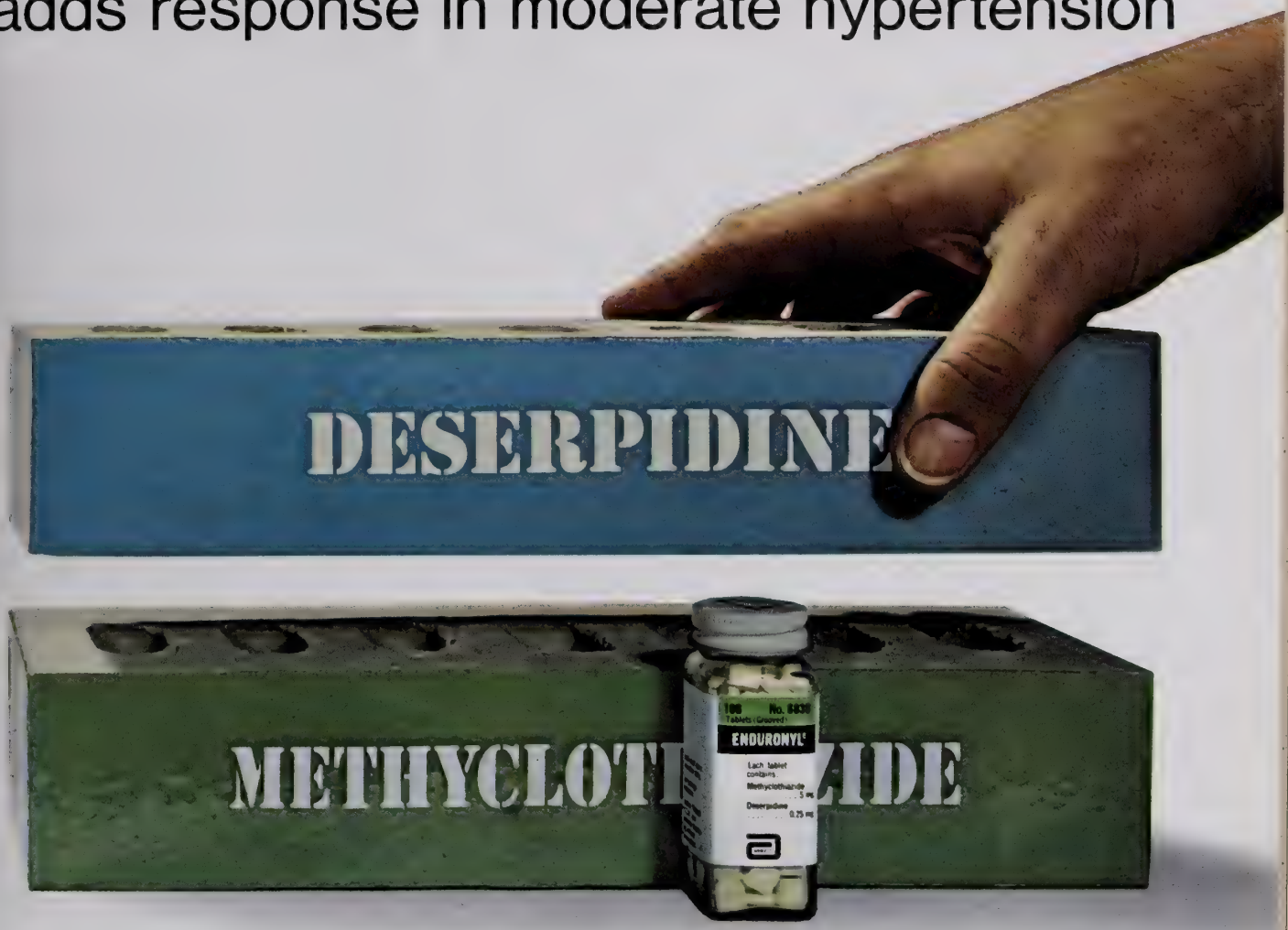
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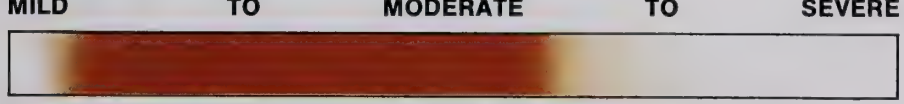
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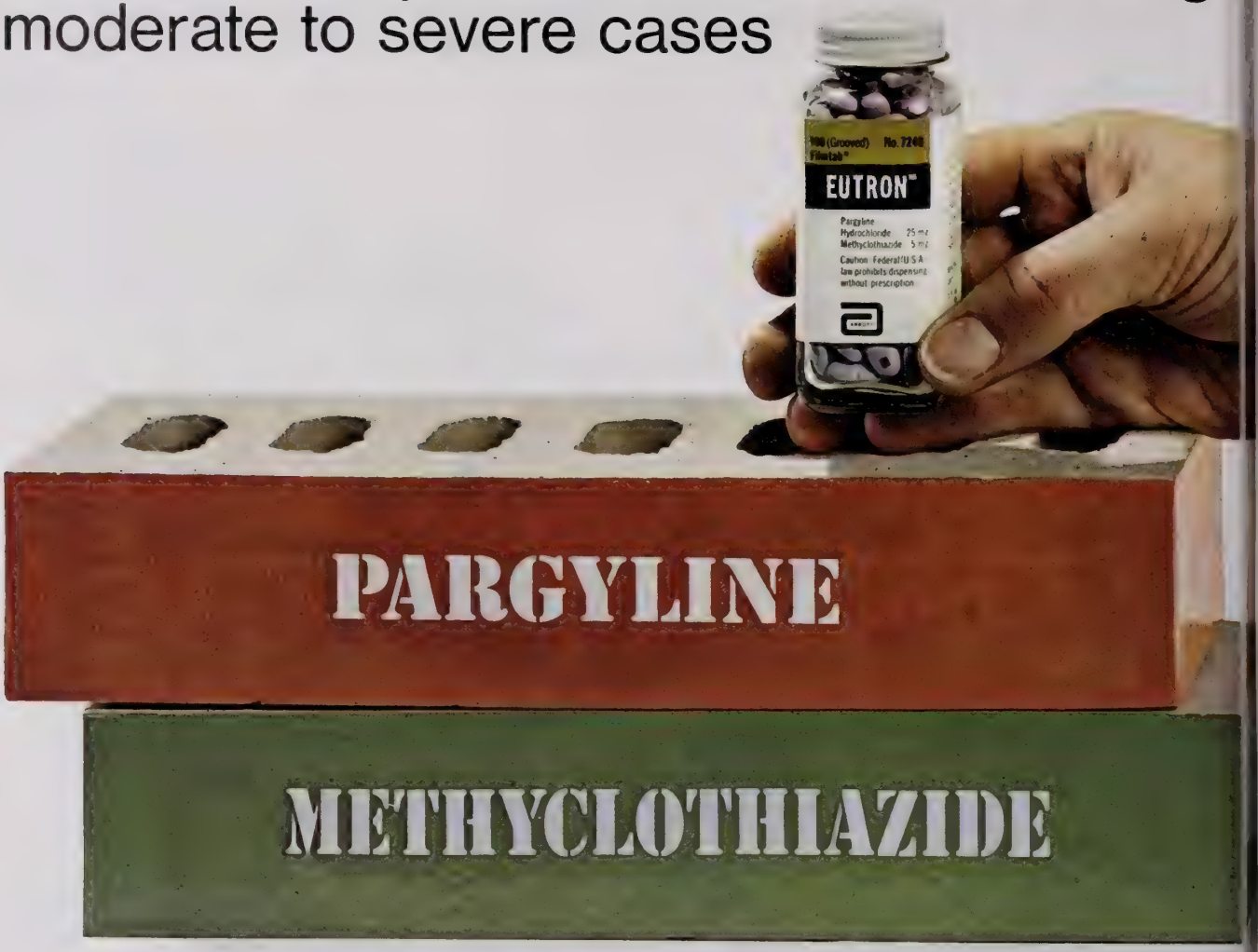
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Warnings: Consider possible sensitivity where there is history of allergy or asthma. If added potassium is indicated, dietary supplementation is recommended. Reserve enteric-coated potassium tablets for cautious use only when necessary, as they may induce serious or fatal small bowel lesions (stenosis with or without ulceration), cause obstruction, hemorrhage, and perforation often requiring surgery; discontinue them immediately if abdominal pain, distention, nausea, vomiting, or g.i. bleeding occurs. Neither Enduron nor Enduronyl contains added potassium.

Precautions: Use thiazides cautiously in severe renal dysfunction, impaired hepatic function or progressive liver disease; also in pregnancy (bone marrow depression, thrombocytopenia, and altered carbohydrate metabolism have been reported in certain newborn). In surgery, thiazides may reduce response to vasopressors, and increase response to tubocurarine. Antihypertensive response may be enhanced following sympathectomy. Watch for electrolyte imbalance (e.g., hyponatremia) in all patients. In hypokalemia (especially in digitalized patients) give supplemental potassium. In hypochloremic alkalosis, give supplemental chloride.

Use rauwolfias with caution in patients with history of peptic ulcer. Rauwolfias with anesthetics may produce hypotension and bradycardia. Discontinue Enduronyl two weeks before elective surgery. Consider vagal blocking agents during emergency surgery. In epilepsy, adjust anticonvulsant dosage. In electroshock, shorten stimulus strength and duration. In occasional patients with depressive tendencies, rauwolfias may precipitate severe mental depression that usually disappears when drug is stopped.

Adverse Reactions: Thiazide reaction include blood dyscrasias (thrombocytopenia with purpura, agranulocytosis, aplastic anemia); elevation of BUN, serum uric acid or blood sugar; anorexia, nausea, vomiting, diarrhea, headache, dizziness, paresthesia, weakness, skin rash, photosensitivity, jaundice, symtomatic gout, and pancreatitis. Cutaneous vasculitis in the elderly has been reported with other thiazides. Adverse effects with deserpidine are qualitatively similar to those with reserpine, but their incidence is lower. These include nasal stuffiness, abdominal cramps or diarrhea, nausea, headache, weight gain, reduced libido and potency, peptic ulcer aggravation, epistaxis, skin eruption, asthma in susceptible patients, electrolyte imbalance, excessive salivation, and a reversible Parkinson's syndrome. Excessive drowsiness, fatigue, weakness, and nightmares may signal mental depression. Thrombocytopenia, purpura, and a symptom manifested by dull sensorium, deafness, uveitis, glaucoma, and optic atrophy are rare allergic reactions to other rauwolfias. Hypotension from antihypertensive agents may precipitate angina attacks in susceptible individuals. Usually adverse reactions disappear when drug is withdrawn.

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Indications—Moderate to severe hypertension.

Contraindications—Pheochromocytoma, paranoid schizophrenia, hyperthyroidism and advanced renal failure. Not recommended in malignant hypertension, children under 12, pregnant patients.

Do not use with: centrally or peripherally acting sympathomimetic drugs; foods high in tyramine (e.g., aged and natural cheeses); parenteral reserpine or guanethidine; imipramine, amitriptyline, desipramine, nortriptyline or their analogues; other monoamine oxidase inhibitors; methyldopa or dopamine; separate Eutron and these agents by two weeks.

Sensitivity to thiazides; severe renal disease (except nephrosis) or shutdown; severe hepatic disease; impending hepatic coma from thiazide-induced hypokalemia.

Warnings—Patients: 1. No other drugs (particularly "cold preparations" and antihistamines), cheese or alcohol without physician's consent. 2. Promptly report orthostatic symptoms, severe headache, other unusual symptoms. 3. Angina pectoris or coronary artery disease patients must not increase physical activity with improved anginal symptoms or well-being.

Physicians: 1. Use antihistamines, hypnotics, sedatives, tranquilizers and narcotics (meperidine contraindicated) cautiously in reduced doses. 2. Stop Eutron two or more weeks before elective surgery; in emergency surgery reduce premedication (narcotics, sedatives, analgesics, etc.) to 1/4 to 1/5; carefully adjust anesthetic dosage to patient response. 3. Use cautiously in advanced renal failure. 4. Pargyline may induce hypoglycemia. 5. Consider possible sensitivity reactions when a history of allergy or asthma is present. 6. If potassium is indicated, dietary supplement is recommended; enteric-coated potassium tablets may induce serious or fatal small bowel lesions (stenosis with or without ulceration), cause obstruction, hemorrhage, and perforation frequently requiring surgery; discontinue medication immediately if abdominal pain, distention, nausea, vomiting or gastrointestinal bleeding occurs; Eutron does not contain added potassium. 7. Possible systemic lupus erythematosus has been reported for thiazides.

Precautions—Pargyline: Use cautiously at reduced dosage: caffeine, alcohol, antihistamines, barbiturates, chloral hydrate, other hypnotics, sedatives, tranquilizers, narcotics. Periodically do urinalyses, blood counts, liver function tests, etc. Use with caution in liver disease. Watch for orthostatic hypotension, especially in impaired circulation (e.g., angina pectoris, coronary artery disease, cerebral arteriosclerosis); also, augmented hypotension in concomitant febrile illnesses. Reduce or discontinue if hypotension is severe. In impaired renal function watch for cumulative drug effects, elevated BUN and other evidence of progressive renal failure; withdraw drug if these persist. In surgery increased central depressant response (hypotension and increased sedative effect) can be controlled by (1) discontinuing at least two weeks prior; (2) in emergency surgery lowering dose of premedication; (3) when necessary, administering a vasopressor. Do not use in hyperactive and hyperexcitable patients. Pargyline may unmask severe psychotic symptoms where emotional problems pre-exist. Use cautiously in Parkinsonism, especially with antiparkinsonian agents. In prolonged therapy, examine for change in color perception, visual fields, fundi and visual acuity. Also, prolonged therapy has made certain patients refractory to nerve blocking effects of local anesthetics.

Methyclothiazide: Use cautiously in severe renal dysfunction, impaired hepatic function or progressive liver disease; also in pregnancy (bone marrow depression, thrombocytopenia, and altered carbohydrate metabolism have been reported in certain newborn). In surgery thiazide may reduce vasopressor response and increase tubocurarine response. Antihypertensive response may be enhanced following sympathectomy. Watch for electrolyte imbalance (e.g., hyponatremia). Give supplemental chloride if hypochloremic alkalosis occurs and supplemental potassium if hypokalemia occurs (especially in digitalized patients). Thiazides may decrease serum P.B.I. without signs of thyroid disturbance.

Adverse Reactions — Pargyline: Orthostatic hypotension and associated symptoms, mild constipation, fluid retention, edema, dry mouth, sweating, increased appetite, arthralgia, nausea, vomiting, headache, insomnia, difficult in micturition, nightmares, impotence, delayed ejaculation, rash, purpura, weight gain, hyperexcitability, increased neuromuscular activity and other extrapyramidal symptoms. Drug fever is extremely rare. Reduction in blood sugar and hypoglycemic effects are possible. Congestive heart failure has been reported in a few patients with reduced cardiac reserve.

Methyclothiazide: Blood dyscrasias (thrombocytopenia with purpura, agranulocytosis, aplastic anemia); elevation of BUN, blood sugar or serum uric acid (gout may be induced); anorexia, nausea, vomiting, diarrhea, headache, dizziness, paresthesia, weakness, skin rash, photosensitivity, jaundice and pancreatitis. Cutaneous vasculitis in elderly patients has been reported with other thiazides.

If side effects are severe or persist, reduce dosage or withdraw drug. 804438R

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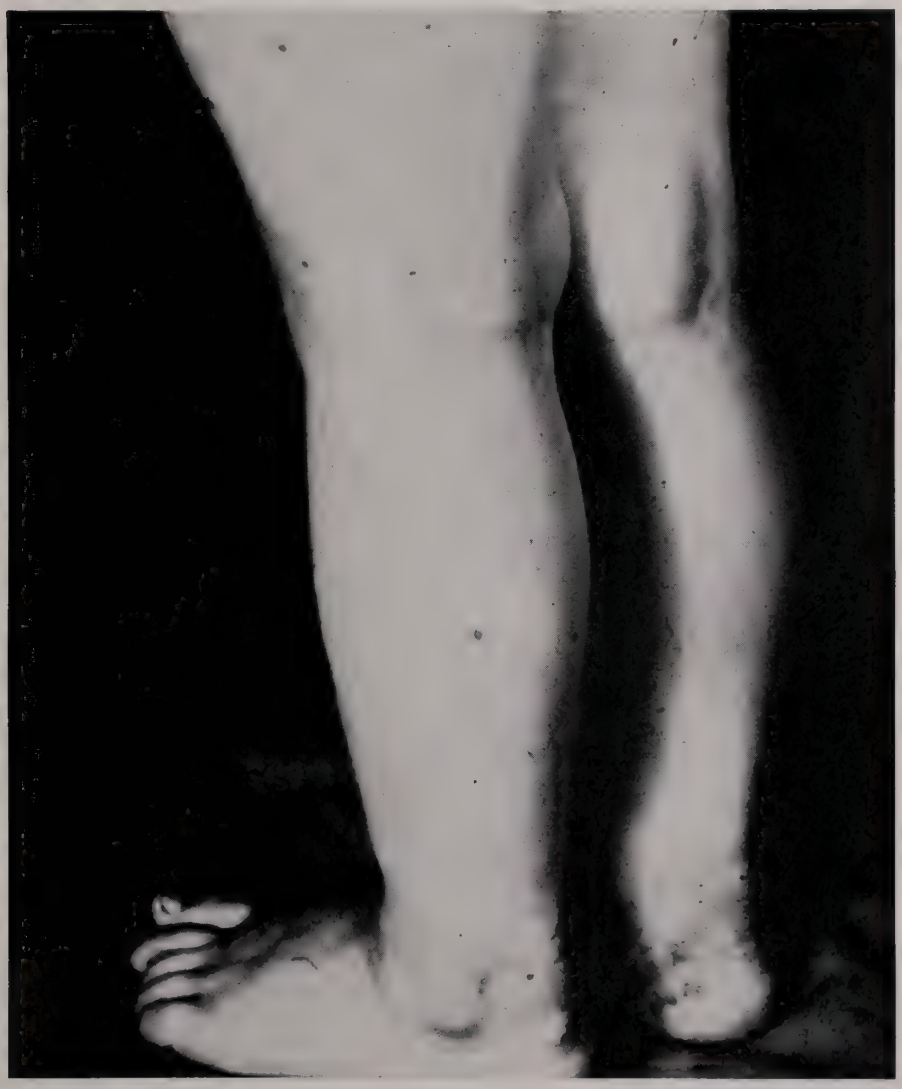
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Dermatology

Swimmer's Itch and Seabather's Eruption

SWIMMER'S ITCH and seabather's eruption, although occurring in different geographical locations, often show similar clinical features. Swimmer's itch is acquired during the summer months by persons swimming or wading in certain lakes of Minnesota, Wisconsin and Michigan. Although seabather's eruption is most common along the Gulf and Atlantic Coasts of Florida from March to September, the patient may present himself to a northern physician on returning from travel. Both eruptions may puzzle those unfamiliar with the clinical picture of each disease.

Swimmer's itch (cutaneous schistosomiasis) is caused by a parasite, the definitive host most often being wild ducks and small rodents. The eggs from the adult schistosome are passed in the excreta of the host and infect the



Figure

fresh water snail, which serves as the intermediate host. When the water temperature rises, the snail releases the cercariae which then come in contact with and invade the swimmer's skin. The clinical picture and symptomatology depend on the person's previous exposures, the initial exposure producing only minor symptoms. Seven to ten days after swimming in infested water, erythematous papules develop on areas that have been submerged. However, areas covered by bathing suits are spared. In about two weeks the cercariae are cast off. With each subsequent exposure, the symptomatology is accelerated and intensified. An initial mild itching sensation lasting for a few minutes to an hour is followed in 10 to 12 hours by discrete, very pruritic papules which may become urticarial or even vesicular (Figure). Generalized urticaria, including unexposed areas, may occur in highly sensitized individuals. The eruption subsides after a few days.

Treatment, which is symptomatic, includes systemic antihistamines and soothing shake lotions. In severe and widespread eruptions, systemic steroids may be used. Preventive measures include thorough washing, preferably with a rough washcloth or towel or with a brush, and vigorous drying as soon as possible after exposure.

The cause of seabather's eruption is unknown. Schistosomes, jellyfish, men-of-war, algae and seaweed have all been mentioned as possible etiologic agents, but none has been documented. Within a few hours after the person leaves the water, erythematous pruritic papules and wheals develop on covered parts of the body; this is in contrast to swimmer's itch where covered areas are spared. The eruption progresses to crusted and vesicular papules resembling insect bites. Systemic symptoms such as chills and fever may be experienced. The lesions spontaneously disappear in seven to 10 days.

Treatment consists of oral antihistamines, corticosteroids, and soothing lotions and creams. Prophylaxis includes avoiding infested water and drying vigorously after leaving the water.

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Shakespeare: Pharmacologia

Hebenon*

"Sleeping within my orchard,
My custom always in the afternoon,
Upon my secure hour thy uncle stole,
With juice of cursed hebenon in a vial,
And in the porches of my ear did pour
The leperous distilment; whose effect
Holds such an enmity with blood of man,
That swift as quicksilver it courses through
The natural gates and alleys of the body;
And with a sudden vigour it doth posset
And curd, like eager droppings into milk,
The thin and wholesome blood: so did it mine;
And a most instant tetter* barked about,
Most lazar-like,* with vile and loathsome crust,
All my smooth body."**

*See Test Your Word Score Page 797.
**Ghost to Hamlet in "Hamlet" I,5.



Grand Rounds

Viral Myocarditis

ERIK E. CARLSON, M.D.
Medical Resident

THE TERM myocarditis was first used in 1837 by Sobernheim[1] to denote inflammation of the myocardium. As used today, however, it refers to the myocardial lesions and clinical picture associated with a variety of infectious diseases, toxins and immune responses, as well as to myocardial inflammatory changes of obscure origin.[2]

Saphir,[3] in a series of 5,626 consecutive autopsies on adults, encountered 240 cases of myocarditis, 186 of which were non-rheumatic. Table 1 is a review of 1,402 cases of myocarditis by Gore and Saphir.[2] These cases, verified at autopsy between 1942 and 1946 at The Armed Forces Institute of Pathology, suggest that a wide variety of etiologic agents and diseases are active in the production of myocarditis. Of these, 70 (5%) are viral in origin. Other authors[4] suggest the incidence of general myocarditis to be as high as 7 to 10% of autopsies done on patients dying of infectious disease. The incidence increases with the number of blocks of tissue removed from each heart for microscopic examination[6] with the thoroughness of the pathologic examination.

Myocarditis

In a clinicopathologic study of thirty-three fatal cases of Asian influenza, Oseasohn et al. found typical microscopic changes in 14 of 33 cases.[5] Walsh et al.[6] found that four of 34 patients with Asian strain influenza developed serious cardiovascular symptoms. Silber[7] reports a series of 21 cases of myocarditis and two of pericarditis, six of which were associated with significant rises in antibody titers for influenza A and B in the period 1950-1956. Finland et al.[8] report two cases of non-bacterial myocarditis in which influenza A virus was isolated from the lungs.

*Presented as a Medical Grand Rounds at Hennepin County General Hospital, February 6, 1968.

In Acute Anterior Poliomyelitis

Teloh[9] reviewed 47 fatal cases of acute anterior poliomyelitis autopsied between 1942 and 1951 and found 26 (55%) of 47 showed an acute myocarditis by microscopic examination of routine histologic sections. Further, during the year 1949 the incidence of myocarditis was 100% of all autopsied cases, suggesting the presence of a viscerotrophic strain of virus with a predeliction for the myocardium. Weinstein,[10] in a review of cardiovascular changes occurring in poliomyelitis, suggested the changes might be due either to direct viral invasion or indirectly via secondary effects on the nervous system, with persistent hypertension, shock, or prolonged anoxia secondary to respiratory insufficiency.

In Mumps

Roberts and Fox[11] report a case of mumps with death from congestive heart failure eight months after the clinical infection. Necropsy showed hypertrophy and interstitial myocardial fibrosis, leaving little doubt as to the pre-

TABLE I

Diseases Associated with Myocarditis* (From Gore and Saphir, 1948)

	1	2		1	2
Rickettsial diseases			Septicemia		
Scrub typhus	227	227	Streptococcus	11	23
Epidemic typhus	23	48	Staphylococcus	34	107
Rocky Mountain spotted fever	9	19	Pneumococcus	9	18
Diphtheria	144	221	Other acute bacteremias	15	Unknown
Subacute bacterial endocarditis	208	208	Acute glomerulonephritis	14	160
Rheumatic heart disease	130	130	Acute tonsillitis	12	Unknown
Meningococcemia	111	256	Acute nasopharyngitis	41	Unknown
Scarlet fever	24	44	Cellulitis, lymphangitis, and wound infections	13	Unknown
Weil's disease	7	8			
Relapsing fever	6	11	Tularemia	1	16
Syphilis (gummatous)	2	66	Brucellosis	2	4
			Miscellaneous (postinfectious)	13	Unknown
Chagas' disease	1	1			
Schistosomiasis	5	41	Exfoliative dermatitis	7	44
Malaria	5	135	Arsenical reaction	1	18
Trichinosis	2	2	Sulfonamide hypersensitivity	105	Unknown
Acute encephalitis	13	144	Disease unknown (so-called "idiopathic")	43	
Poliomyelitis	13	94			
Infectious mononucleosis	6	9	Starvation	33	50
Measles					
Guillain-Barre syndrome	3	30			
Mumps	1	8	Heat stroke		
Epidemic hepatitis	1	400	Surviving less than 24 hours	16	45
Smallpox	1	9	Surviving more than 24 hours	13	26
Virus pneumonia	32	222	Carbon monoxide poisoning (limited to patients who survived for an appreciable interval after the lethal exposure)	1	30
Tuberculosis	9	581	Emetine	1	70
Boeck's sarcoid	3	12	Burns	11	45
Coccidioidomycosis	11	48			
Blastomycosis	2	5	Total	1402	
Actinomycosis	1	9			
Torulosis	1	6			

*The figures in the first column represent the number of times myocarditis was encountered. Whenever possible the number of cases of each disease, screened to ascertain the first figure, is given in column 2. The ratio of the two thus provides a crude index of the frequency of myocarditis in each disease.

**Amer Heart J 34:827, 1947.

sence of preceding myocarditis. Other observers[12] report a 5 to 7% incidence of electrocardiographic changes in patients during mump epidemics. Atrioventricular dissociation associated with Stokes-Adams syndrome, presumably secondary to mumps myocarditis, was satisfactorily treated with a transvenous pacemaker by Nolan and Thompson.[13]

In Other Diseases

Garrison and Swisher[14] used adrenocorticotropic hormone in the treatment of intractable heart failure in a myocarditis of unknown etiology with good clinical result. Viral studies were not done.

Hall and Finegold[15] found transient electrocardiogram abnormalities with ST-T wave changes, ectopic beats and conductive delay in six of 20 patients *with Reiter's syndrome.*

Friedburg[16] suggests that a *post-infection myocarditis* may result from a hypersensitivity reaction in which a virus, or other agent, "by altering the antigenic properties of the heart or by acting in conjunction with anti-heart antibodies" could produce an auto-immune reaction.

Kline et al.[17] report two patients with *endocardial fibroelastosis* and discuss related research in dogs. They offer evidence that endocardial fibroelastosis is related to chronic myocarditis and secondary cardiac lymphatic obstruction or to chronic lymphatic obstruction of any other etiology.

McNally and Qamer[18] report a case of *generalized vaccinia* which developed a loud pericardial friction rub and ST-T changes of an acute pericarditis. This was rapidly resolved with the administration of vaccinia immune globulin.

As previously noted,[2] other viral infections including *infectious mononucleosis, encephalitis, and hepatitis* have also been implicated in the production of a myocarditis.

The spectrum, then, of myocardial disease secondary to viral infections is broad and highly variable. Nevertheless, most observers will agree on the basic production of a myocarditis whether it is in origin, infectious, toxic or auto-immune, following a virus infection.

Pathology

Gross examination of the heart reveals nonspecific "toxic" changes with a flabby, yellowish to pallid myocardium and biventricular dilation. Mural thrombi may be present. Not infrequently, however, the heart may appear relatively normal to gross examination.

Cut surfaces may reveal subepicardial and subendocardial petechiae and hemorrhagic extravasation, as was reported in six cases by Oseasohn et al.[5]

Microscopic

Histologically the lesions include focal or diffuse invasion of the interstitial tissue with lymphocytes and monocytes and less commonly polymorphonuclear cells. A variable degree of interstitial edema may be present. Plasma cells and necrosis of muscle fibers are not prominent. If the infiltration is sparse and focal, the cellular reaction may be perivascular with a relatively normal adjacent myocardium.[4-5]

One observer reports four patients in whom the myocardial arteriols showed fibrinoid degeneration with focal fibrin mural thrombi in the involved vessels.[5]

Clinical Diagnosis

The clinical diagnosis of a viral myocarditis is frequently one of inference or association of non-specific cardiac signs in the presence of a suspected viral disease.

Signs[19]

Sinus tachycardia (rarely bradycardia)
Abnormal rhythms, including gallop rhythm
Enlargement of the heart
Faint or snapping quality of the first heart sound
Cardiac insufficiency
Defective intraventricular or atrioventricular conduction and abnormal final ventricular deflections (S-T and T)
Increased serum glutamic oxaloacetic transaminase
Constitutional and special manifestations of the basic infection (fever, leukocytosis, increased sedimentation rate, increased C-reactive protein, positive blood culture)

The clinical features of 33 fatal cases of Asian influenza[5] are summarized in Table 2. Other observers[4,6,7,20] support the variable symptomatology and occasionally fulminating course with rapid progression to death that these cases represent. Not infrequently, this may be due to the acute myocarditis, with consequent heart failure, arrhythmias and cardiac arrest being the terminal event.

Abelman[20], in an excellent general review of myocarditis, suggests that frequently myocarditis is not recognized clinically, even in the presence of signs of cardiac involvement, because these signs are frequently overshadowed by the manifestations of the primary, systemic disease.

Abelman further suggests that sub-clinical myocarditis may be a common accomplice of viral infections in view of the frequently focal nature of the pathologic findings at autopsy. Consequently, unless such focal lesions produced major derangements of conduction, or arrythmias, the large organ reserve the heart possesses would allow relatively normal cardiac function to continue. The addition, however, of a pre-existing cardiovascular stress, such as anemia, fever, alcoholism, hypervolemia, hyperthyroidism, work and pregnancy may lead to rapid decompensation and cardiac failure.[20]

Electrocardiogram

Electrocardiographic changes in viral myocarditis cover a wide spectrum of abnormalities (Tables 3, 4). Disturbances of rhythm are common. Silber[7] found first-and second-degree A-V block and bigeminy (due to ventricular premature systoles) to predominate in his series of 23 patients. Other arrythmias included atrial ectopic beats, nodal tachycardia and any form of sinus arrythmias. Sinus bradycardia has been reported,[6] as has third-degree A-V block.[13]

Changes of contour including non-specific ST-T changes, left heart strain, ischemia, pericarditis, and wandering pacemaker have been reported.[4,6,7,21]

Vectorcardiograms were done in 20 patients by Walsh et al.[6] who found that in 16 of 20 patients the afferent limbs of QRS loops were distorted. At the peak of illness, four patients demonstrated arching similar to that ob-

served in diaphragmatic myocardial infarction. These changes resolved with convalescence.

Therapy

Although it is not possible to treat viral myocarditis specifically, many diseases causing an acute myocarditis *are* treatable and should be carefully

TABLE 2*
Clinical Features of 33 Fatal Cases of Asian Influenza

Case No.	Age	Sex	Race	Date of Death	Clinical Data
2	22	M	N	10/1	Sudden onset of influenza-like illness; patient admitted to hospital with signs of bilateral pneumonitis; died despite cardiac-resuscitation attempt.
6	10	M	N	10/10	Sudden onset of influenza-like illness with epistaxis; 7 siblings of patient simultaneously ill.
12	21	M	W	10/17	Patient returned home from work because of influenza-like illness; found dead in bed that night.
14	47	F	W	10/17	Sudden onset of influenza-like illness; bilateral pneumonitis developed; chronic rheumatic mitral stenosis, uncomplicated heart failure.
15	48	M	N	10/19	Patient sent home from work because of influenza-like illness; found dead in bed that night.
16	77	M	W	10/20	Sudden onset of influenza-like illness, with increasing congestive heart failure; arteriosclerotic heart disease with remote healed infarct; adenocarcinoma of colon.
20	31	F	W	10/25	Patient found dead on floor of home on day after complete dental extraction under inhalation anesthesia.
27	9	M	W	11/5	Mild coryza, followed on third day by convulsions, extensor spasm, fever and coma; patient died one hr. after onset of seizure (known to have epilepsy).
31	17	M	W	11/18	Onset of "cold"; rapid development of dyspnea, tachypnea, cyanosis & signs of bilateral pneumonitis.
3**	32	F	N	10/4	Influenza-like illness for four days; patient admitted to hospital on fourth day in extremis with signs of bilateral pneumonitis and meningismus.
4	24	F	N	10/7	Sudden onset of influenza-like illness, followed by pneumonitis, in fifth month of pregnancy; chronic rheumatic mitral stenosis uncomplicated by heart failure; patient died despite steroid therapy.
5	17	F	N	10/8	Sudden onset of influenza-like illness, with signs of bilateral pneumonitis; patient died despite steroid therapy.
8	44	F	W	10/13	Influenza-like illness for one wk.; patient found dead in bed (chronic alcoholism with liver cirrhosis).
9†	51	M	W	10/13	Vague influenza-like illness for one wk.; patient continued to work; found dead at home.
7†	23	F	N	10/13	Patient six months pregnant; sudden onset of influenza-like illness with spontaneous abortion on third day; sudden collapse on sixth day; died despite steroids and cardiac-resuscitation attempt.
10†	13	M	W	10/15	Influenza-like illness followed by seizures, coma and fever; lumbar puncture negative.
11	16	M	W	10/16	Sudden onset of influenza-like illness, signs of bilateral pneumonitis on third day; patient found dead in bed on fourth day.
13	73	M	W	10/17	Patient, aged widower living alone, sick for five days; no other history; found dead in bed.
18	9/12	F	N	10/22	Coryza followed by vomiting & diarrhea; patient found dead in bed.

*New Engl J Med 260:509, 1959.
**Tissues not tested for virus.
†Virus-negative cases.

ruled out in the workup. Every effort should be made to identify the specific organism involved.

The presence of heart failure suggests the usual supportive measures, including bed rest, salt restriction, diuretics, O_2, cardiac glycosides and phlebotomy as indicated.

Bed Rest

Bed rest, in the presence of a myocarditis, is specific and important therapy. Experimental studies with mice[22,33] show that strenuous activity in the form of forced swimming in mice infected with coxsackie A9 virus, strain 13, lead to both cardiomegaly and enhanced viral replication. Similarly, mice infected with the parasite trypanosoma cruzi, when forced to exercise, also showed an increase in cardiac to body weight ratios and increased numbers of parasites.

Digitalis

The presence of increased myocardial irritability suggests that when used, digitalis should be given (1) in submaximal amounts, (2) as the shorter

TABLE 3*

Summary of Electrocardiographic Findings in Patients with Viral Myocarditis

Contour abnormalities alone	11
Contour abnormalities with arrhythmias	7
Arrhythmias only	1
Questionable abnormalities	1
	20**

Types of Electrocardiographic Abnormalities in Patients with Viral Myocarditis

Contour Alterations	With Complete Restitution†		Arrhythmias (All Transient)	
Nonspecific S-T T changes	5	2	1st or 2nd degree A-V block	5
Left heart strain‡	3	0	Bigeminy (due to vent. prem. systoles)	2
Ischemia†	1	1		
Subacute pericarditis	5	2	Other (auric. prem. systoles, tachycardia,	
Combinations of above‡#	4	3	or fibrillation, nodal tachycardia)	4

*Ann Intern Med 48:232, 1958.

**In three of the total of 23 cases studied, serial electrocardiograms were lacking.

†Primarily in the presumptive group.

‡Left heart strain patterns, isolated or in combination, were not in the influenza group.

#Ischemia patterns seen only in three cases associated with lobar pneumonia.

TABLE 4*

Summary of Electrocardiographic Changes in 12 Patients Who Had Asian Influenza

Illness	Recovery
1. S-T depression in Lead III	Normal
2. Slight S-T elevation in Leads V_{4-5}	S-T elevation in Lead V_4
3. Normal	S-T depression in Lead II
4. S-T elevation in Lead V_8	S-T elevation in Leads $V_{4,5}$
5. S-T elevation in Leads $V_{2,3,4}$	S-T elevation in Leads $V_{4,5}$
6. T flat in Leads I, II, III, V_6	T flat in Lead V_6
7. T flat in Leads $V_{5,6}$	Normal
8. T flats in Leads $V_{4,5,6}$	Normal
9. T flat in Leads $V_{4,5,6}$	T flat in Leads $V_{4,5,6}$
10. Normal	Wandering pacemaker
11. Normal	Wandering pacemaker
12. Normal	High nodal rhythm

*Amer Heart J 57:667, 1959.

acting preparations, and (3) with frequent monitoring of the electrocardiogram.

Control Arrythmia

Arrythmias should be controlled where possible with agents such as xylocaine, procaine amide, quinidine, or dilantin.

Complete A-V block is, as always, an indication for electrical pacing if unresponsive to atropine and isuprel.

Steroids are controversial. Experimentally they seem to enhance viral replication[24] and reduce intrinsic host resistance in mice.[25] However, in the hands of clinicians, steroids appear to have been lifesaving in the treatment of viral myocarditis with intractable heart failure. Ainger[26] reports a series of eight children treated for periods varying from 42 to 145 days, with uniformly good responses.

Case Report

History of Present Illness

This was the first Hennepin County General Hospital admission for this 44-year-old negro male. The patient gave a history of two weeks of progressive ankle swelling, shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, and a weight loss of approximately 20 pounds over the previous past two and one-half months. He had a medical history of drinking three pints of hard liquor, three to four pints of wine, and one-half case of beer per week. His medical history also revealed treatment for gonococcal infections eleven times with penicillin, and treatment for syphilis in 1943 with heat therapy.

Physical Examination on Admission

The blood pressure was 120/90, the apical rate 130 per minute and irregular. The chest showed fine moist diffuse rales at the bases and to the level of the scapulae bilaterally. No murmur was noted, but there was a protodiastolic gallop present. The point of maximum impulse was prominent in the anterior axillary line. The liver was not palpable but was percussable four fingerbreadths below the right costal margin and not tender. The spleen was not palpable. Extremities showed 4+ pitting edema to the knees. The remainder of the physical examination was unremarkable.

Hospital Course

On admission the patient's chest x-ray showed massive cardiomegaly with the cardiothoracic ratio approaching 70%. The pulmonary vasculature was prominent and there was an alveolar infiltrate consistent with a pulmonary edema. Venous pressure on admission was 22 cm. Circulation time was 75 seconds arm-to-tongue with a very sharp end point. Cardiac fluoroscopy showed a very quiet heart without evidence of calcification. A CO_2 infusion study of the heart was within normal limits. A radioactive iodine-tagged albumin scanogram of the heart was also found to be within normal limits. A paradoxical pulse was not present. The patient, however, continued to run a very narrow pulse pressure in the range of 20 mm. of mercury throughout his hospital stay. Laboratory data on admission showed a hemoglobin of 14.9 with a total white count of 3,600 cells. Differential showed 42 neutrophils, 52 lymphocytes and 6 eosinophils. Antistreptolysin O titer on admission was 50 Todd units. The sedimentation rate was 14. Lupus erythematosus tests were negative. Serum glutamic oxaloacetic transaminase on admission was 32, rising to a high of 85 units and sinking slowly back into the range of 20-30 units. Acute and convalescent sera for viral studies were sent to the State Boards and showed the following:

	Dec. 13	Dec. 26	Jan. 19
Hemagglutination-Inhibition Titer A_2.....	1/20	1/640	1/1280
Complement Fixation Adenovirus	1/8	1/8	1/8
Cold Agglutinins	1/64	1/128	1/128

Attempts at isolating the virus from the patient's sputum to date have been unsuccessful,

On admission the patient's weight was 206 pounds. He was put on a regimen of 500 mg. salt-restricted diet, treated vigorously with diuretics, digitalis and placed on strict bed rest. On this regimen his weight steadily decreased to 159½ pounds ten days after admission. Multiple electrocardiograms were done. In general, these tracings showed a sinus rhythm with left axis deviation, left ventricular hypertrophy, left ventricular strain, and a first-degree A-V block. The QRS complex was 0.10 seconds in duration and was thought by some to show an incomplete left bundle branch block. A vectorcardiogram on January 17, 1968, showed left ventricular hypertrophy. Chest x-rays on serial examination showed a slow decrease in the size of the heart over the period of hospitalization. On January 9, 1968, the circulation time had decreased to 45 seconds and the venous pressure was 11 cm. On January 23, 1968, the circulation time was down to 20 seconds with the venous pressure 9.8. The patient has continued to have intermittent gallop rhythm, and at the time of this summary still shows a cardiothoracic ratio of 60%.

Diagnosis

1. Acute viral myocarditis influenza Type A-2.
2. Chronic alcoholism.

References may be secured from the Grand Rounds Editor.

The Pickled Brain

None of our family on either side, so far as I can find out, had ever practiced medicine. My own experience of doctors had been a chequered one, but at my father's suggestion I gladly went up and discussed the matter with our country family doctor.

The only remaining memory of that visit was that the old doctor brought down from one of his shelves a large jar, out of which he produced a pickled human brain. I was thrilled with entirely new emotions. I had never thought of man's body as a machine. That this weird, white-puckered-up mass could be the producer or transmitter of all that made man, that it controlled our physical strength and growth, and our responses to life—why, it was absolutely marvelous.

My father saw at once on my return that I had found my real interest, and put before me two alternative plans, one to go to Oxford, where my brother had just entered, or to join him in London and take up work in the London Hospital and University, preparatory to going in for medicine. I choose the latter at once—a decision I have never regretted.*

*Wilfred T. Grenfell (1865-1940) in Why We Became Doctors, edited by Noah D. Fabricant, M.D., 1954.

Editor's Note: Wilfred Grenfell established the Labrador mission in Newfoundland, later extending his mission service to six hospitals, seven nursing stations, four hospital ships, four orphanges, fourteen industrial centers, three agricultural stations, and twelve clothing distribution centers. He was knighted by George V.

Sorrel cleanses the body of feculent humours—if the plant be eaten green or its juice drunk, it helps an offensive breath, fastens loose teeth, cures the putrefaction of the gums, and is extremely beneficial in all cases where the blood is too fluid and the vessels lax.—Boerhave

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That man can interrogate as well as observe nature was a lesson slowly learned in his evolution.—Osler



Abstracts, Briefs and Commentaries

CARCINOMA OF THE PENIS IN A JEW CIRCUMCISED IN INFANCY

There are only four authenticated cases of carcinoma of the penis occurring in Jews circumcised at birth. Wolfarst reported a case in a non-circumcised Jew. Margolis records a case of a carcinoma of the penis in a Gentile circumcised at birth, not documented, however. Lecklider reported four cases in Hebrews, but the circumcision statuses are not known.

Ewing quoted Bessesen: "Carcinoma of the penis is unknown to the Jewish race. It is commoner in other races and obviously due to the irritation of decomposing smegma and infection."

Case Report

A Jewish male, 65 years of age, was ritually circumcised on the eighth day after birth. He is married but has no children. He has had no venereal disease.

For over 10 years he has had an irritating lesion at the base of the glans. During the last three years this has progressed to a warty growth which left a bleeding base when it flaked off. There was a papillary growth seen on examination, and an area of hyperkeratosis on the corona. No inguinal glands were palpable.

The growth and the hyperkeratotic area were excised. Histological examination revealed a squamous-celled carcinoma of unusually pronounced papillary structure. Radio therapy was given to the shaft and glans. There has been no recurrence after six years.

Summary

A case of carcinoma of the penis in a Jewish male circumcised at birth is presented. This is only the fifth case recorded.

Stanley R. Maxeiner, Sr., M.D.
Minneapolis, Minnesota

Melmed, Edward P. and Pyne, John R.: Carcinoma of the Penis in a Jew Circumcised in Infancy. Charing Cross Hospital, London.

GANGRENE OF THE HAND FOLLOWING INTRA-ARTERIAL INJECTION

Three patients had inadvertent injection of intravenous drugs into an artery of an upper extremity. Each resulted in gangrene of portions of the hand, resulting in later amputation. The drugs involved were amobarbital

sodium, meperidine HCl and promethazine mixture, and promazine HCl. Despite immediate local and general therapy, gangrene was not avoided. The clinical picture is characteristic: immediate pain in the arterial distribution and various reactions of the skin and pulses. Awareness of aberrant locations of the upper extremity arteries, poor lighting, failure to inject a small test dose, and not checking for pulses distally are probable factors to correct for prevention.

Jerome T. Grismer, M.D.
Minneapolis, Minnesota

Hager, D. L. and Nelson, J. N.: Gangrene of the Hand Following Intraarterial Injection. Arch Surg 94:86, 1967.

First London Pharmacopoeia

In 1618 the First London Pharmacopoeia appeared, now considered the outstanding event in pharmacopoeia making. It was not the initial pharmacopoeia, for in 1498 one had been issued in Florence, another in Barcelona in 1535, followed during the sixteenth century by John Jacob Wecker's "antidotary," the compilation of formulas by Valerius Cordus in Nuremberg, in 1546, and the Augsburg Pharmacopoeia in 1564. The thousands of formulae printed in these pharmacopoeias were those of the authorities of the past such as Galen, Avicenna, Rhazes and Nicholas Preapositus. The first London Pharmacopoeia, sponsored by the College of Physicians in London, recorded every known remedy of the ancients with great catholicity and also included many prescriptions attributed to contemporary authorities. It contained 1,028 simple drugs and 932 preparations. Many revolting substances are listed as well as medicines familiar today, such as potassium bitartrate, sulphur, potassium nitrate, calomel, lead acetate, antimony oxide, aloe, calcium hydroxide, scamony and squill.

That the popular use of bizarre medication continued is evidenced by the cures recommended by the standard reference works of the eighteenth century such as Zedler's Universal Lexicon and Chamber's Cyclopedia. The former declares that an ape's heart, roasted, dried and pulverized, strengthens the heart and dispels melancholy; that the ashes of a stork distilled into an essence is effective against poisons and the pest; that the brain of a dog of solid color, when cooked and eaten, dispels delirium caused by the bite of a mad dog; that the gall of a black suckling dog ground into a powder or mixed with vinegar is a cure for apoplexy, lethargies and vertigoes. In 1739, Joanna Stephens sold to Parliament for five thousand pounds her remedy for stone, which was endorsed by Cheselden, Sharp and Hawkins. Upon analysis, it proved to be a "mixture of egg shells, garden snails, swine's creasses,* soap and such vegetable ingredients as burdock seeds,* hips and haws.**

*See Test Your Word Score Page 797.
**Bernhard Stern: Society and Medical Progress, 1941.

Sorrel

Sorrel sharpens the appetite, assuages heat, cools the liver, and strengthens the heart; it is an anti-scorbutic, resisting putrefaction, and in the making of sallets imparts a grateful quickness to the rest as supplying the want of oranges and lemons.—John Evelyn



Book Reviews

Books, the children of the brain.—Swift

CLINICAL HEMATOLOGY—Maxwell M. Wintrobe, M.D.: New 6th edition. Pages XXV plus 1287. Total illustrations 278. In color 76 on 21 plates. Price: $22.50. Lea and Febiger, Philadelphia 1967.

Dr. Wintrobe has rewritten better than 50 per cent of the text. He has added many new black and white figures and some new tables, and he has revised others. Electron photomicrographs are presented of ribosomes, a basophilic erythroblast, a reticulocyte, an expelled erythroblast nucleus, and a myeloblast. Additional electron photomicrographs of megakaryoblasts, lymphoblasts, monoblasts, myeloma cells, plasma cells, and megaloblasts would have enhanced the value of the book for students. The photomicrographs of cells in Plates III, V, XV, and XVIII lack morphologic sharpness and color differentiation. Plates IV, VI, VII, IX, XIII, XIX, and XXI show color drawings of cells that represent an artist's concept rather than the actual microscopic appearance.

The chapter "The origin and development of the cells of the blood in the embryo, infant and adult" has been extensively revised, and the section "Cytology and molecular aspects of cell growth and development" is new.

The methods of Berman and Axelrod, and those of the reviewer are combined into one procedure for the preparation of sections from aspirated material (page 31). The method as described needs revision. The thickness of the outer lamina of the sternum is given as 0.2 to 5 mm. and for the depth of the cavity 5 to 15 mm. (page 30). These measurements differ from those recorded by this reviewer of 0.8 to 1.5 mm. for the lamina and 6 to 9 mm. for the cavity (Minnesota Med 49:1321, 1966). Correctness of such data is important to the inexperienced operator, because he can easily push the needle through the entire bone, particularly when it is osteoporotic.

In the chapter "Principles of technic of blood examination" the directions read: "If the stain is an aqueous one and preliminary fixation is necessary, this may be accomplished by heating the slides at 120° to 125° C. for a few minutes; or passing them through a small flame 3 or 4 times." Procedures such as these produce undesirable cellular and staining artefacts.

Dr. Wintrobe has brought up to date "Pernicious anemia and related macrocytic anemias." To this chapter he appends "Hereditary orotic aciduria," a condition which may produce megaloblastosis refractory to vitamin B_{12} therapy but responding to uridine.

The chapter "Paraproteinemias" is new. Color photomicrographs of myeloma cells and lymphoid cells, the latter characteristic of Waldenström's macroglobulinemia, are shown in Plate XX.

For students to appreciate the morphology of Sternberg or Reed-Sternberg cells, color or black and white photomicrographs should have accompanied the chapter "Conditions chiefly affecting lymph nodes and the spleen." Dr. Wintrobe states in the section "Infectious mononucleosis:" "In spite of the failure to identify the agent most investigators now believe that infectious mononucleosis is caused by a virus, but this must be one which is very delicate, easily destroyed and transmitted only with difficulty, possibly by intimate contact." Recent research on the Epstein-Barr virus by J. C. Niederman et al. (JAMA 203:205, 1968) suggesting an etiologic role for this virus in this disease unfortunately was published too late to be cited in the book. The article, however, by Dr. A. C. P. Campbell (J Path Bact 60:629, 1948), the first investigator describing reticulum hyperplasia, proliferation of pleomorphic lymphoid cells, and presence of granuloma-like structures in the marrow of patients with Pfeiffer's glandular fever (infectious mononucleosis), should have been cited in the bibliography.

E. M. Schleicher, Ph.D.
Minneapolis, Minnesota

HANDBOOK OF FRACTURES—By Ralston. Publication date: November, 1967. Price: $10.75. C. V. Mosby Company, 299 pages, 156 illustrations.

This small but compact text should appeal to the medical student and intern for it is very readable, amply illustrated, and not verbose. The author has done an admirable job of presenting the major points and principles of treatment of the commonly seen fractures.

It is noteworthy, also, that the author has included in each section a lucid review of the relevant anatomy and physiology in order that the reader might be better prepared to render effective treatment.

Harrison H. Farley, M.D.
Minneapolis, Minnesota



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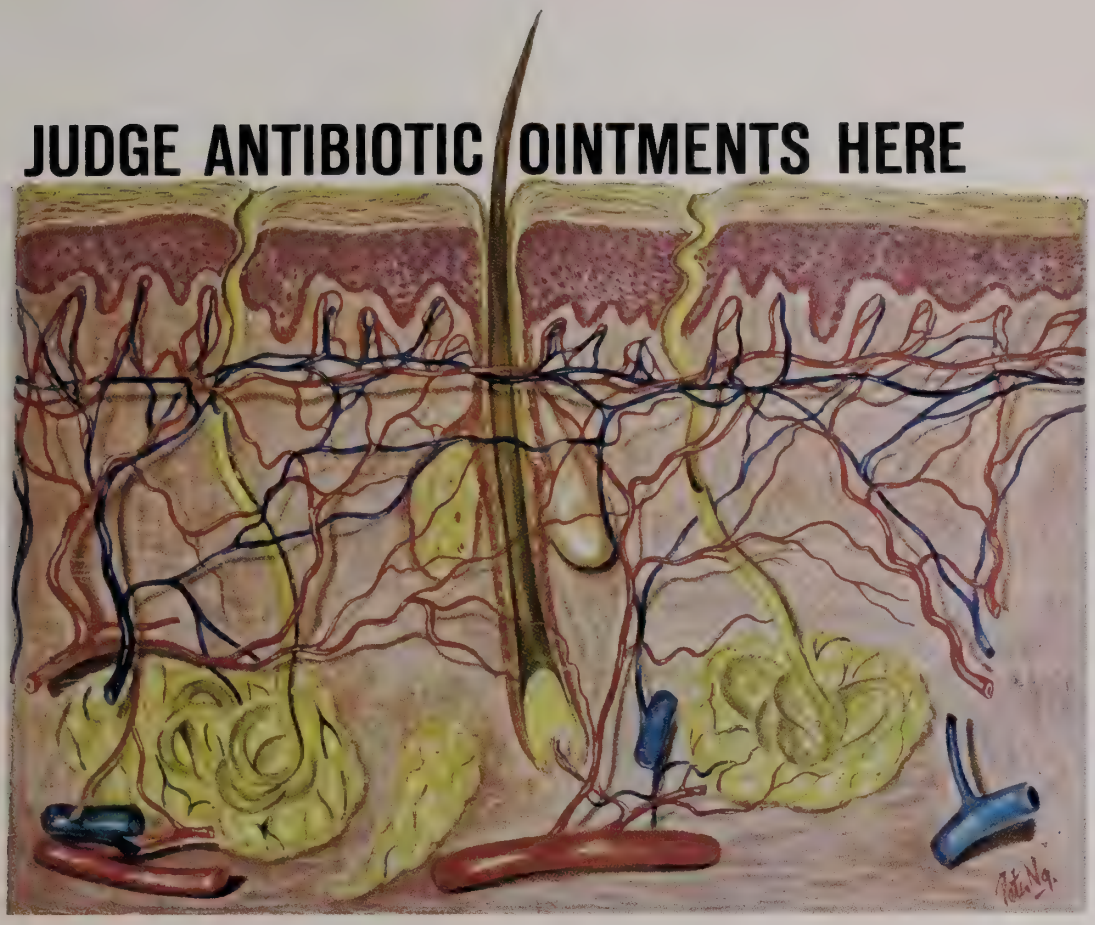
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Complete blood and platelet counts should be done prior to and at regular intervals during treatment with the drug (see recommendations under "Important Note and Precautions") to help in the early detection of serious bone marrow injury. Abnormalities in initial blood tests should rule out use of the drug. Also, patients should be made aware of such early toxic signs of a potential hematologic problem as fever, sore throat, mouth ulcers, easy bruising and petechial or purpuric hemorrhage. Should such signs appear, the patient should be advised to discontinue the drug and to report to the physician immediately.

Indication Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia. It is not a simple analgesic and should never be administered for relief of trivial facial aches or pains.
Contraindication Do not use in those with a known sensitivity to any tricyclic compound or in those being treated with M.A.O.I. agents. As long a period as possible should elapse before using Tegretol in patients who have been treated with M.A.O.I.'s, with a minimum of 7 days. In such cases, initial dosage should be low and the patient's reaction to gradual increments closely observed.
Important Note and Precautions Familiarity with the clinical symptoms which lead to an accurate diagnosis of true trigeminal neuralgia and with the complete prescribing information, careful patient selection, a thorough examination before treatment and close patient supervision throughout the treatment period are essential to the safe and effective use of this drug.
Where feasible, Tegretol should not be used in conjunction with any potent drug which may increase the possibility of toxic reactions.
In pregnancy, the drug should not be prescribed during the first trimester and thereafter only to patients in whom the clinical situation warrants the potential risk. It should not be administered to nursing mothers.
Patients with increased intraocular pressure should be closely observed during treatment with this drug because of its anticholinergic effect.
Because of the drug's relationship to other tricyclic compounds, the possibility of activation of latent psychosis and, in the elderly, of confusion or agitation, should be considered.
Dizziness and drowsiness may occur and patients should be cautioned about the hazards of operating machinery or automobiles and of engaging in other hazardous tasks.
Use cautiously in patients with a history of coronary artery disease, organic heart disease, congestive failure or liver disease.
Before initiating therapy, the following laboratory procedures should be performed:
1. Complete blood and platelet counts which, if abnormal, should rule out the use of the drug.
2. Baseline evaluations of liver function.

During treatment with Tegretol, the following laboratory procedures should be performed:
1. Complete blood and platelet counts should be done at intervals of one week during the first month of drug treatment, every two weeks during the second and third months, and at monthly intervals thereafter for as long as the patient is taking the drug. A trend toward a decreasing white blood cell count should suggest a dosage reduction and more frequent laboratory and clinical evaluations. Should this trend continue, the drug should be discontinued.
2. Liver function tests must be performed at regular intervals during treatment with this drug since liver damage may occur during therapy. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.
3. Periodic eye examinations, including slit-lamp, funduscopy and tonometry, are recommended for patients being treated with this drug since many phenothiazines and related drugs have been shown to cause eye changes.
4. Complete urinalysis and BUN should be done on patients treated with Tegretol because of observed renal dysfunction.

Adverse Reactions Dizziness, drowsiness, unsteadiness on the feet, nausea, vomiting, aplastic anemia, transitory leukopenia, agranulocytosis, eosinophilia, leukocytosis, thrombocytopenia, purpura, abnormalities in liver function tests, cholestatic and hepatocellular jaundice, urinary frequency, acute urinary retention, oliguria with elevated blood pressure, albuminuria, glycosuria, elevated BUN, microscopic deposits in the urine, impotence, disturbances of coordination, confusion, headache, fatigue, blurred vision, transient diplopia and oculomotor disturbances, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, nystagmus, tinnitus, paralysis and other symptoms of cerebral arterial insufficiency, pruritic and erythematous rashes, urticaria, Stevens-Johnson syndrome, photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, alopecia, diaphoresis, recurrence of thrombophlebitis, erythema multiforme and nodosum, aggravation of disseminated lupus erythematosus, gastric distress, abdominal pain, diarrhea, constipation, anorexia, dryness of the mouth and pharynx, glossitis, stomatitis, fever, chills, adenopathy, lymphadenopathy, aching joints and muscles, leg cramps, conjunctivitis, left ventricular failure, aggravation of hypertension, hypotension, syncope and collapse, edema, aggravation of coronary artery disease and congestive heart failure. (Whether these cardiovascular effects are drug-related is not known. However, some of these complications have resulted in fatalities.) The necessity for discontinuing the drug should be dictated by the gravity and severity of the adverse reactions.
Dosage and Administration The drug should always be taken with meals, if possible.
Initial: One-half tablet (100 mg.) b.i.d. on the first day. Thereafter, the dose should be increased in one-half tablet (100 mg.) increments every 12 hours until freedom from pain is achieved. To relieve pain, between 200 mg. and 1200 mg. per 24 hours may be necessary.
Maintenance: Initial control of pain can be maintained in most patients with a dose of 400 mg. to 800 mg. daily. Maintenance doses may range between 200 mg. and 1200 mg. daily.
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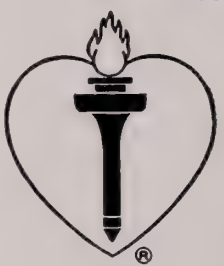
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Address

General Hospital Must be Saved*

Mayor Arthur Naftalin

FIVE YEARS AGO we were embroiled in a hard-fought but successful struggle to save General Hospital. Now the existence of General Hospital is once again threatened and unless we act quickly we could lose this magnificent institution.

To close General Hospital would be a community disaster, the result of the public's failure to appreciate the indispensable functions the hospital performs.

In the past five years the need for General has not diminished; it has grown. This is especially significant because five years ago there were many predictions that, with the coming of Medicare, much of the need for General would fade away.

But General has continued to grow because it provides a broad variety of services that people need. It continues to build a fine reputation as a treatment and training center, handling in sympathetic and dedicated fashion the medical requirements of a large segment of our city's population.

General Hospital has been a major institution for 80 years, but many citizens still have only a partial awareness of how the institution is organized and of the services and functions it performs.

Its operation involves the delicate meshing of many resources, all of which are essential for its continued success.

The Staff

The permanent full-time staff of 49 specialists is employed jointly by the County and the University of Minnesota; they direct the work of the residents, interns, undergraduate medical students and other technical personnel in various stages of training.

Residents

The staff includes 66 residents. They are engaged by the county, but they also have status as medical fellows at the University of Minnesota, an arrangement that serves to attract men and women of unusually strong ability, who come to us because they are seeking opportunities for advanced training in all the specialized services that make up the broad practice of medicine. It is estimated that 45 per cent of all specialists and 25 per cent of all general practitioners in Hennepin County received all or part of their training at General.

Interns

The intern group that complements the residency staff currently numbers 48. In the past fifteen years, General has been one of only three large hospitals in the United States that *never failed* to fill its entire intern quota. During this period it has filled a toal of 606 rotating internships.

*Presented to The Forty-Eighth Annual Senior Meeting of the Minneapolis Academy of Medicine. Monday, January 15, 1968. The Minneapolis Club.

Paramedical Personnel

But General Hospital trains not only doctors. It also trains annually 600 students as hospital and medical specialists—nurses, laboratory technicians, x-ray technicians, anesthetists, medical and psychiatric social workers, psychologists, pharmacists, physical therapists and hospital administrators.

Finally, the entire training program has the continuing participation of 334 community physicians. These practitioners contribute thousands of hours of free service in caring for patients and in teaching residents, interns, clerks, and technicians. This provides a measure of medical consultation available at very few other medical centers.

It is the combination of these several levels of professional personnel that makes General Hospital the outstanding medical center it is. The county provides the facility and the patients, the University of Minnesota assists in organizing the medical program and in attracting needed professional staff, and the community provides the reservoir of medical knowledge and experience. All these balanced elements are essential for the hospital's success.

If General Should Die

Private Hospitals

If General should die, could our private city hospitals attract a similar complement of 114 young American medical trainees? Consider these facts: It has been estimated that our city's private hospitals are now spending five dollars a day or more per patient to hire training chiefs and run educational programs to attract interns and residents. How are they faring?

St. Barnabas and Swedish Hospitals sought 20 interns this year; they will have nine, all foreign graduates from the Philippines, India and Latin-America; and there will be twelve residents, nine of them foreign. Northwestern sought 12 interns and obtained four, two foreign; it also has two residents from India. Mt. Sinai has four interns and 19 residents, all but one foreign; Fairview has five residents, all foreign; St. Mary's had 14 openings and filled 11 of them with Americans.

The word "foreign" is not used here in a demeaning sense but to emphasize that foreign graduates do not usually practice here after they complete their training. In contrast, American doctors tend to settle not where they attend medical school but where they complete their final training, whether it be internship or residency.

The Emergency Role

Many of our private hospitals now plan to expand their training facilities, and it is only fair to say that they may be able to attract more interns and residents than formerly.

But the judgment of leading medical men in our area is that it would be tragic to take General out of the mainstream of producing our area's physicians. Furthermore, they maintain that our private hospitals are not really geared to handling General's 24-hour-a-day emergency role as a county hospital facility. During 1967, General handled a total of 70,000 separate emergencies, providing care without reservation, to anyone in need, regardless of residency.

The city's other emergency facilities located at Southdale, North Memorial and Methodist, are all private facilities and are not geared to handle the number of emergencies that General does.

Yet General's emergency role is only one of its many vital functions.

Its Role for the Welfare Agencies

The average bed capacity at General is 394; its average annual occupancy is 80 per cent. Occupancy is lowest (50 to 70 per cent) in pediatrics and obstetrics, a fact which bespeaks the changing and aging character of our population; occupancy exceeds 90 per cent in surgery, trauma (accidents) and male medical wards; and it ranges substantially upwards of 100 per cent in psychiatry, which means beds overflowing in halls and aisles. Five operating rooms work around the clock to do 3,700 procedures annually; private hospitals would use 10 to 14 rooms for the same load.

The hospital provides care for patients in categorical aid programs and in Medicare and for those referred to it by other welfare agencies such as the Hennepin County Welfare Board which then reimburses the hospital.

Contagious Diseases

General also cares for patients with contagious diseases. Such cases are often ex-

tremely difficult, disruptive, or dangerous for the voluntary hospital to provide adequate facilities to isolate and treat. Among the contagious diseases treated in 1967 were meningitis, tuberculosis, gonorrhea, syphilis and hepatitis.

Dialysis Center

General has three other functions I would like to describe very briefly. First, General offers a comprehensive variety of services that any private hospital would be hard put to duplicate. It is the nation's second largest dialysis center for impaired kidneys; it provides special services in hyperbaric medicine, which is that ultra-modern high pressure facility for surgery to force oxygen into body cells and tissues under the same kind of pressure as is exerted 66 feet beneath the sea.

Disaster Center

General Hospital has intensive care units for massive burns and coronary cases; it is an effective suicide prevention center with a special phone that rings many times a day; it is also our area's poison control center.

Second, General is very much an outpatient hospital. It acts as family physician to over 40,000 persons in our community, who consider it just that in our age of mobile populations with their changing patterns of personal medical care. If General dies, could the physicians of our community handle such an added caseload?

Mental Health Facility

And, third, General is further recognized as one of our nation's leading rescue stations for troubled minds; it is considered one of the ten outstanding mental health services in the country.

It has an absolute open-door policy, providing both outpatient and inpatient psychiatric services to anyone in need, as last year's 19,500 outpatient psychiatric visits will attest. Psychiatry is its one service which is used more by suburban than city residents.

The Cost

Five years ago we shifted management of the hospital from the City to the County. That step was essential at that time; but it accomplished only a part of the job of saving the hospital, and it created some new problems, which are now becoming acute.

It resulted in the introduction of the use principle as the basis for financing the hospital, including the costs of the training program. As a result, Minneapolis taxpayers pay four times as much as suburbanites towards the $13.07 million dollar budget for 1968. City residents will be taxed 14.02 mills on their property taxes; suburbanites, 3.2 mills.

The budget problem is further aggravated in that General cannot continue to operate in its present ugly, aged and obsolete plant much longer. It must either rehabilitate its present facilities, which have been shown to be almost impossible, or build new ones; but the money is simply not in sight. One may legitimately ask if such new and costly facilities are really needed in this day of medicare and hospital insurance when government or insurance paid care is available to most persons in private hospitals? What should its new, expanded role be?

The emphatic answer in my mind is that the hospital is indispensable, but the Planning Agency for the Hospitals of Metropolitan Minneapolis has commissioned a study to determine if the hospital is needed, and, if so, what kind of facilities should be planned.

Although the study findings will not be available until the end of the summer, a public referendum has been ordered for the November 5 election ballot as to whether a new general hospital should be built.

The evidence is almost certain to be overwhelmingly in favor of continuing the hospital; but this study will not be completed until late August, allowing only a few weeks for the public to become familiar with the findings of the study before voting.

Alternative

The referendum should be postponed until at least after the 1969 legislative session, at which the entire matter should be reviewed again.*

General Hospital is more than a county concern. Its loss would adversely affect the entire state and region and would seriously complicate plans presently being considered for develop-

*Editor's note: Since the Mayor's speech, the Board of Hennepin County Commissioners on February 20, 1968, rescinded their prior action calling for a referendum in the fall of 1968 and postponed the referendum until such time as the Board and the community have had sufficient opportunity to consider the findings of the Booz-Allen-Hamilton study.

ment of a new medical school. Its loss would also adversely affect the continued supply of physicians for the state.

Responsibility of the State

The state must recognize a responsibility to ensure the continuation of the institution on a financing basis that is fair and equitable to everyone who benefits from the institution, whether as patient or as member of the public receiving improved medical care as the result of the hospital's world famous training program. It is also essential that action towards a new building be taken quickly, as it is estimated that it will take three to five years to build a new facility, which would bring us to at least 1972-73.

The New Facility

The new facility that must be built will function as a major training center and as a truly, modern comprehensive health center. It should be the central institution for a network that includes satellites serving our new Pilot Center, the Model Neighborhood, and other new social renewal projects.

General's future role might be to serve as a focus for other public health measures, including a much expanded community alcoholic rehabilitation program, offering detoxification treatment of alcoholics. It could also serve for retardation research, drug addiction control, and as a blood testing center for our courts.

Tax Benefits

I know that three voluntary medical complexes are in various stages of planning and that there are some who see these associations assuming some of the functions General currently provides. Whatever these complexes achieve, they will not be able to replace General Hospital.

No voluntary hospital can be given the tax support that General now enjoys. Also, a host of problems relating to liability in the management of public responsibilities and immunity would be difficult for voluntary hospitals to achieve.

Institutional Practice

Unlike our private hospitals to which patients are sent by their own physicians for specific treatment or surgery, General believes in the institutional practice of medicine; it caters to the year-round inpatient and outpatient health needs of the individual—and this is important when we realize that General is basically the hospital of the poor, the medically indigent, and those with only moderate incomes insufficient to pay large medical bills.

At General, all fees depend upon income. In 1964, 78 per cent of General's expenses were contributed by local taxes; whereas in 1968, only 53 per cent were contributed by local taxes. It would further appear that in the future, local taxes for support will be reduced to an even smaller proportion of the total budget, describing as further contributions by other third party payees, such as Medicare, rise. It is significant to note that under all of our categorical aid programs more than 20 per cent of our citizens voluntarily choose General as the hospital to which they *wish* to be sent, despite the opportunity to go anywhere they please.

In the light of all these factors, I believe we must launch a community-wide crusade to support General Hospital—to rebuild it completely, to move it, if necessary, but to keep its location in downtown Minneapolis.

I recommend that we dispense with the referendum, that we enlist instead the cooperation and support of the state legislature in developing a direct and constructive program for the continuing future of the hospital. General should be financed on a countywide basis, with all residents within the county sharing on an equitable basis, because all residents benefit from this institution.

If General dies, some agency, some level of government will still have to provide most of the services—such as those in emergency, contagion, poison control, disaster. This would require new, costly facilities, whether there is a General or not. If General closes at a time when the area population spirals upward, patients throughout the county will quickly feel the impact, in the form of an acute doctor shortage.

Therefore I appeal to all the members of the Academy and to everyone in the medical and allied professions to give unstinting support to an immediate drive for a massive public education campaign on the need to save the General Hospital and to enlist the active backing of local, state and national authorities.

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Warning—In renal impairment, usual doses may lead to excessive accumulation and liver toxicity. Under such conditions, lower than usual doses are indicated, and, if therapy is prolonged, serum level determinations may be advisable. A photodynamic reaction to natural or artificial sunlight has been observed. Small amounts of drug and short exposure may produce an exaggerated sunburn reaction which may range from erythema to severe skin manifestations. In a smaller proportion, photoallergic reactions have been reported. Patients should avoid direct exposure to sunlight and discontinue drug at the first evidence of skin discomfort. Necessary subsequent courses of treatment with tetracyclines should be carefully observed.

Precautions—Overgrowth of nonsusceptible organisms may occur. Constant observation is essential. If new infections appear, appropriate measures should be taken. In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment.

Side Effects—Gastrointestinal system—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin—maculopapular and erythematous rashes; a rare case of exfoliative dermatitis has been reported. Photosensitivity; onycholysis and discoloration of the nails (rare). Kidney—rise in BUN, apparently dose related. Transient increase in urinary output, sometimes accompanied by thirst (rare). Hypersensitivity reactions—urticaria, angioneurotic edema, anaphylaxis. Teeth—dental staining (yellow-brown) in children of mothers given this drug during the latter half of pregnancy, and in children given the drug during the neonatal period, infancy and early childhood. Enamel hypoplasia has been seen in a few children. If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy.

Average Adult Daily Dosage: 150 mg q.i.d. or 300 mg b.i.d. Should be given 1 hour before or 2 hours after meals, since absorption is impaired by the concomitant administration of high calcium content drugs, foods and some dairy products. Treatment of streptococcal infections should continue for 10 days, even though symptoms have subsided.

In the treatment of syphilis a dosage schedule of a total of 12 to 18 Gm given in equally divided doses over a period of 10 to 15 days should be followed. Close follow-up observation of the patient is recommended, including appropriate laboratory tests, since demethylchlortetracycline has not had adequate evaluation in all stages of syphilis. Spinal fluid examination should be included as part of this follow-up.

Acute gonococcal anterior urethritis in males has been treated effectively with a single dose of 600-900 mg of DECLOMYCIN Demethylchlortetracycline. Individuals unable to tolerate large single doses due to gastrointestinal side effects may be treated with 150 mg every 6 hours for a minimum of 4 doses or 300 mg every 12 hours for a minimum of 2 doses. Females should be treated with a dosage of 150 mg every 6 hours or 300 mg every 12 hours until a cure is effected.

Primary Atypical Pneumonia (Eaton Agent): The average adult daily dosage is 900 mg in 3 divided doses for six days.

LEDERLE LABORATORIES, A Division of
American Cyanamid Company, Pearl River, N.Y.

Lederle

379-8

Special Article

Gram-Negative Septicemia

at

St. Mary's Hospital, Duluth, Minnesota*
(1964-1966)

GRAM-NEGATIVE septicemia is a common complication of the hospital environment. Studies in several large centers have listed septicemia as a second most common cause of death among hospitalized medical and surgical patients.[1] The septicemia syndrome is caused by the release into the blood of bacterial endotoxin** which directly and indirectly mediates the development of a characteristic clinical syndrome in many patients.

The effects of the endotoxin-producing bacteria on the human organism are best classified according to the clinical symptomatology exhibited and the course of the illness leading either to death or to recovery. Two classes of response to the septic gram-negative invader emerge.

Class I: Acute Bacteremia

This first category of clinical response to the gram-negative invader may be divided into two distinct types, but for the purposes of this report, both types are recorded under the Class I definition.

Type A, Post-Manipulation Bacteremia, is described by those patients whose presenting symptoms include a fever over 101°, perhaps a shaking chill, diaphoresis, possibly some nausea, a feeling of decreased well being, anorexia and listlessness. The blood culture may not be positive; the bacteremia is episodic and relatively limited in duration and severity; and the recovery is rapid. Aside from fever, leukocytosis, and a positive blood culture, the patient has few laboratory or clinical findings. After one or several episodes, he either spontaneously recovers, or is perhaps treated with a broad-spectrum antibiotic with a prompt fall in temperature and complete recovery. Notably absent in such a patient is hypotension, shock, confusion, tachypnea or collapse.

Type B, Progressive Bacteremia, includes those patients with fever, a severe shaking chill, tachycardia and confusion. Early the skin may be warm and damp; later it will be pale, cyanotic and clammy. Also observed may be moderate tachypnea, moderate hypotension, often nausea, vomiting or diarrhea. Oliguria may be noted. These signs, combined with an anxious expression and restlessness, are clear indicators of an acute, serious illness. Blood cultures are more often positive in this group than in Type A, indicative of greater quantities of bacteria spilled more frequently into the blood stream. Fever, leukocytosis, acidosis, deepening shock and decreasing urinary flow indicate a relentless progression. Untreated, the majority of such patients eventually succumb, usually within 10 days. A few never exhibit hypotension and have relatively warm extremities and adequate urinary output. Yet many of these patients die. In most series, 40-50 per cent in this category do not recover.[1]

Class II: Acute Collapse Reaction

Patients presenting this response are seen as an acute corpulmonale reaction to the presence of endotoxin-producing bacteria in the vascular system.[2] These patients are suddenly critically ill: tachypneic, often deeply cyanotic, confused to comatose, severely hypotensive, with oliguria or anuria, and in complete vascular collapse. Rapid development of acidosis, leukocytosis, electrocardiographic changes suggesting right heart strain, decreased pulmonary vascularity, bronchospasm, and distended neck veins point strongly toward pulmonary embolism as the etiology. However, at post-

*Prize Essay, Duluth Surgical Society, May, 1967.
**See Test Your Word Score Page 797.

mortem examination only a severe infection is present and no emboli are found. This manifestation of gram-negative septicemia has only recently been described, but it may well account for many sudden hospital deaths previously listed as myocardial or pulmonary in etiology. Death occurs in a matter of hours in nearly 100% of such patients.

Materials and Methods

From May, 1964, through December, 1966 70 adult and 14 pediatric patients at St. Mary's Hospital provided 84 positive blood cultures for gram-negative bacteria, based on blood samples drawn before and after death. A relatively consistent distribution of positive cultures was noted, with 17 reported between May and December, 1964, 30 in 1965, and 37 in 1966. The hospital record of each patient was studied to observe the clinical manifestations of the gram-negative septicemia syndrome. Treatment employed was also studied but will not be discussed here. Other valuable information was obtained from the necropsy summary. The clinical manifestations and associations were listed for each patient according to the following definitions:

1. *Presence of a shaking chill* (so described in the nurses' or physicians' notes)
2. *Temperature* (over 101°)
3. *Hypotension* (less than 90 mm Hg)
4. *Tachycardia* (heart rate over 100/minute)
5. *Confusion* (as noted by nurses)
6. *Clinical shock* (cold extremities, diaphoresis, pallor)
7. *Tachypnea* (respiratory rate greater than 26/minute)
8. *Nausea, vomiting or diarrhea*
9. *Reduced renal output* (oliguria - anuria; below 450cc/day)
10. *Indwelling catheter*

Other parameters studied included: (1) the portal of entry of the bacteria, (2) the number of patients falling into Class II, (3) diseases associated, (4) and the relationship between hypotension and death.

Two broad categories of patients, adults, and children were studied. Medical, surgical and Ob-Gyn patients made up the adult group. Because of the great differences in response of infants to septic invaders, the pediatric age group was divided into those patients under one month of age and those over one month.

Results and Discussion

The presence of gram-negative invaders in the blood was best shown to be clinically correlated with three readily measured parameters: temperature, heart rate, and respiratory rate. Eighty per cent of those patients in the study had a temperature over 101° (Table 1). Seventy-seven per cent had a heart rate over 100, and 71 per cent a respiratory rate greater than 26/minute. Temperature is the most valuable clinical indicator of sepsis; if it is very high, especially in the elderly, a diagnosis of septicemia is probable. Confusion is another prominent symptom, especially in the elderly patient who was lucid before the onset of septicemia. Children over one month of age present essentially the same

TABLE I
Clinical Signs in Gram-Negative Septicemia
Adults

Clinical Sign	Medicine	Surgery	Ob-Gyn	Totals	Per Cent
Shaking Chill	18	13	4	35	50
Temp. over 101°	33	16	7	56	80
Hypotension	17	7	0	24	34.3
Tachycardia	32	15	7	54	77
Confusion	29	11	2	42	60
Clinical shock	20	6	1	27	38.6
Tachypnea	30	16	4	50	71.4
Nausea, etc.	22	5	2	29	41.4
Catheter	22	17	5	44	62.8
Oliguria	10	10	0	20	28.6
Deaths	24	11	2	37	52.9
Recovered	17	10	6	33	47.1
Number patients	41	21	8	70	100.1

picture as adults.

Clinical Symptoms

Children less than one month of age exhibit few of the classical signs of septicemia. Table 2 illustrates the paucity of symptoms found in the infant in the presence of septicemia. Tachypnea occurred in 60 per cent of the patients in this group and was the only symptom present in several cases. None had a temperature over 101°. Only one infant had a shaking chill and only two had a tachycardia. Other factors, such as neonatal jaundice, poor eating, and failure to thrive, were more often seen. Persistent tachypnea in the very young child should encourage a search for sepsis.

The classical "shaking chill" occurred in 50 per cent of the adults but in only 10 per cent of the infants. Its presence is pathognomic of a septicemia and in most cases was recognized as such. Although this symptom is very helpful in diagnosis, it should *not* be relied upon as the most sensitive indicator of sepsis.

TABLE 2
Clinical Signs in Gram-Negative Septicemia
Children

Clinical Sign	Under one month of age	Per Cent	Over one month (to age 16)	Per Cent
Shaking chill	1	10	1	25
Temp. over 101°	0	0	3	75
Hypotension	0	0	1	25
Tachycardia	2	20	3	75
Confusion	....	....	3	75
Clinical shock	0	0	2	50
Tachypnea	6	60	1	25
Nausea, etc.	0	0	2	50
Oliguria	0	0	0	0
Catheter	0	0	2	50
Deaths	7	70	2	50
Recovered	3	30	2	50
Number patients	10	100	4	100

The Organisms

Eleven different organisms in pure culture and several mixed gram-negative infections were found in adults (Table 3). Nearly 45 per cent of adult gram-negative septicemias were caused by E. coli. Proteus species were a distant second with a 15 per cent rate of occurrence. E. coli affected 60 per cent of the new-born group (in pure culture) while an additional 20 per cent were found to have a mixed infection with E. coli one of the agents. Opportunistic, normally saphrophytic organisms, like Pseudomonas species were found in significant association with lymphomas and terminal metastatic disease.

Portal of Entry

The portal of entry of the gram-negative invader was most often the urinary tract (Table 4). The presence of an indwelling catheter should be kept in mind when a source for sepsis is sought. Nearly 25 per cent of the bacteria gained entrance through the peritoneum; 15 per cent came from other areas (skin, bowel, bones, etc.), and only 10 per cent of adults showed no obvious avenue of sepsis. Thus a diligent search by the clinician is most often rewarded.

TABLE 3
Organisms

Agent	Adults	%	Children (over 1 mo.)	%	Children (under 1 mo.)	%
Eschereschia coli	31	44.3	1	25	6	60
Proteus species	10	14.3	1	25	1	10
Bacteroides	5	7.2	0	0	0	0
Klebsiella	5	7.2	0	0	0	0
Pseudomonas aeruginosa	4	5.7	1	25	0	0
Aerobacter aerogenes	3	4.3	0	0	0	0
Mimea polymorphia	2	2.9	0	0	1	10
Salmonella typhosa	1	1.4	0	0	0	0
Salmonella typhimurium	1	1.4	0	0	0	0
Salmonella chester	0	0	1	25	0	0
Pseudomonas multifida	1	1.4	0	0	0	0
Soil bacteria	1	1.4	0	0	0	0
Mixed flora	6	8.6	0	0	2	20

Associated Disease

In 39 per cent of the cases, adult sepsis was associated with disease which, in itself would often be fatal. Fourteen individuals had cancer, many in advanced stages of the disease. Two patients had cirrhosis, five diabetes mellitus, and six others a chronic debilitating disease such as multiple sclerosis. Many of these patients had indwelling catheters, constituting a ready beach-head for bacterial invasion. Early diagnosis and treatment of such patients may result in added months or years of useful life.

Morbidity

Twenty-four of the adults developed hypotension during the course of their septicemia. Of these 24, 21 died (86.6 per cent). Many of these patients did not receive heroic treatment; but in spite of heroic measures, no authors have reported salvage of more than 50 per cent of these patients. Bearing in mind the possible disastrous effects of spillage of bacterial organisms into the blood, early treatment of known gram-negative infections (such as cystitis and pyelonephritis) will do much to lessen the incidence of such severe reactions.

Twelve patients presented the Class II or Acute Collapse Reaction, one of whom survived. Three were infants less than two weeks of age. Two case reports of patients whose responses fall into Class II are illustrative of what the clinician might find on the ward.

Case Reports

Case 1

A 69-year-old Indian woman was brought to the St. Mary's Hospital emergency room comatose and in shock on 9/8/66. The patient had been found in this condition in bed at home. In February, 1966, she had had an open reduction of a subtrochanteric fracture of her right hip. During that admission an indwelling Foley catheter had been used for ten days without complication. All laboratory reports had been within normal limits. The patient had had a previous history of Potts disease, and numerous cultures of sputa for acid-fast bacilli had been negative. She had been discharged in April, 1966. On her 9/8/66 admission the patient was deeply comatose, pale, cold and clammy; the blood pressure was unobtainable; the pupils were dilated and fixed. The heart rate was 82 and regular. Respirations were 26/minute and described as "short." An electrocardiogram showed sinus arrhythmia. The white blood cell count was 14,600; the differential: 5 myelocytes, 7 metamyelocytes, 17 non-segs, 29 segmented forms, 36 lymphs, and 6 monocytes. The hemoglobin was 16.3 —121%. Twenty-five minutes after admission respiration ceased and she could not be revived. The attending physician felt that she died of a massive cerebrovascular accident. At necropsy over 1000 colonies of E. coli per cc. were cultured from the blood. Acute bilateral pyelonephritis with bilateral necrotizing papillitis and chronic cystitis were found.

Comment: The death of this patient in a matter of hours illustrates the overwhelming effect of endotoxin on the body integrity of some patients. This patient was not acutely tachypneic on admission, not described as being in deep cyanosis, but was in profound peripheral vascular collapse. The significant left shift of the differential white blood cell count and the hemoconcentration suggest an acute hypovolemia. This picture is often seen in gram-negative septicemia with shock and forms part of the basis for treatment with plasma, dextran and other volume expanders as proposed by several authors.[1,3,4]

Case 2

A 57-year-old white woman with a diagnosis of acute lymphatic leukemia, in protective isolation, developed right pleuritic chest pain at 9:00 a.m. on 12/1/66. She was acutely dyspneic, cyanotic, restless and dizzy. The blood pressure was 70 systolic, 50 diastolic; the heart rate was 150; the respirations were 36-48/minute; the temperature was 104°. A chest film showed a right middle lobe and left lower lobe infiltrate. Massive doses of penicillin, chloromycetin, fluids and isoproterynol were used in treatment. The dyspnea and cyanosis deepened, and the patient expired with extreme tachypnea and cyanosis at 8:00 p.m. that night, 11 hours from the onset of

TABLE 4
Portal of Entry

Route	Adults	%	Children (over 1 mo.)	%	Children (under 1 mo.)	%
Urinary Tract	35	50	1	25	0	0
Peritoneum	17	24.3	0	0	0	0
Other (skin, lung GI, ortho, etc.)	11	15.7	1	25	8	80
Unknown	7	10	2	50	1	10

the illness. Blood cultures drawn before and after the antibiotic regimen was begun, grew out more than 1000 colonies of *Pseudomonas aeruginosa*. At necropsy bilateral bronchopneumonia, acute lymphatic leukemia and a massive Pseudomonas septicemia were found.

Comment: The ease of confusion with pulmonary embolism in this patient is apparent. Others in Class II presented a similar picture. If pulmonary embolism is suspected but the temperature is elevated, sepsis should be entertained as a probable etiology for the clinical state and heroic measures of treatment begun.

Of the eight adults and four children shown to manifest the severe reaction of Class II, only one adult survived. This patient was treated with massive doses of broad-spectrum antibiotics, large doses of steroids, and intensive nursing care. After several days she responded and recovered uneventfully. Thus, although a Class II reaction to gram-negative septicemia carries a grave prognosis, early and persistent therapy may result in an occasional survival.

The number of diagnostic impressions listed in the 12 patients in Class II is almost as long as the list of patients. Several were thought to have pulmonary embolism and one a cerebrovascular accident; in others the attending physician ascribed a myocardial etiology as the prime diagnosis. In most of the patients the diagnosis was made at necropsy. Other severe disease processes were present, concurrently, in several patients. Two had leukemia, one patient acute pancreatitis and fatty cirrhosis, one a perirectal abcess, and one acute bilateral pyelonephritis.

Conclusions

Eighty-four blood cultures at St. Mary's Hospital, Duluth, Minnesota, (drawn from 84 patients) were positive for gram-negative organisms between May, 1964, and December, 1966. The charts and/or necropsy summaries on each patient were reviewed, noting the clinical course, the bacteria involved, the portal of entry, the treatment, and the prognosis. The following salient conclusions can be drawn:

1. Elevated temperature, tachycardia, tachypnea and confusion occur more often in the presence of a gram-negative septicemia than does the classical shaking chill.
2. Children under the age of one month present with different symptomatology than older children and adults.
3. The main portal of entry of gram-negative bacteria remains the urinary tract.
4. Hypotension occurring during the course of a gram-negative septicemia indicates a grave but not hopeless prognosis.

Two broad classes of response to the invasion of the gram-negative bacteria into the blood can be listed. The first class is best considered in two subclasses: Type A, Post Manipulation Bacteremia, and Type B, Progressive Bacteremia. The second Class, Acute Collapse Reaction, includes patients with a much more fulminant reaction. Two cases in this group are presented. It is postulated by the author that several similar cases of sepsis might pass unnoticed each year in the average 500-bed hospital, the clinical diagnostic impression being pulmonary embolism, massive cerebrovascular accident, or massive myocardial infarction.

Lt. Frederick E. Ludwig, II, M.D.
MC USNR
San Francisco, California

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2. Cor pulmonale in Endotoxin Shock. The Lancet No. 7442. Apr 16, 1966.
3. Lillehei, R. C.: Shock—Current Concepts of Pathogensis and Treatment. The New Physician, pp. 415, November, 1964.
4. MacLean, L. D. et. al.: Treatment of Shock in Man Based on Hemodynamic Diagnosis. Surg Gyn & Obstet 150:1, 1965.

Half our mistakes in life arise from feeling where we ought to think, and thinking where we ought to feel.—John Churton Collins

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Men will wrangle for religion; write for it; fight for it; die for it; anything but live for it.—Charles Caleb Colton

Popular Fallacies

Settlers Guessed About Medicine

American medical tradition stems from an age very different from the one in which we now live, points out TODAY'S HEALTH GUIDE, the American Medical Association's manual of health information for the American family.

The early settlers, living remote from civilization, turned to the traditions of their ancestral homelands and to the methods of the Indians, and came up with a medical lore all their own. Their ideas of prevention and treatment were not all wrong, but often they did more harm than good. Some of the common misconceptions of the frontier era have carried over into modern times.

TODAY'S HEALTH GUIDE lists the facts about some of these misconceptions—

- Blood pressure of 100 plus the individual's age is *not* the normal value.
- Red meats and alcohol are *not* necessarily harmful to those with high blood pressure.
- Fish is *not* a brain food, it is simply a good food for all parts of the body.
- Sweets, while possibly detrimental to the teeth, are *not* the sole cause of tooth decay.
- There is no reason of health why one should not eat shellfish and ice cream at the same meal, provided neither of them is spoiled.
- Lemons, oranges, tomatoes and grapefruit do *not* cause "acidity" of the body.
- Fat people are *not* necessarily carefree and jolly.
- Being fat and 40 and feeling well does *not* constitute a good reason for declining to lose weight.
- It is *not* necessarily unwise to drink water with your meals, if you don't gulp it.
- Gargles and mouthwashes do *not* kill the germs in the mouth or throat.
- Boils are *not* due to impure blood.
- Punctures from rusty nails are no more dangerous than punctures from shiny nails; the danger lies in the germs that either one may introduce.
- Night air is *not* unhealthful. However, it is *not* necessary to open the windows of your bedroom wide at night, especially when it is cold.
- Whiskey with aspirin is *not* a good remedy for a cold. The cold might improve in spite of it.

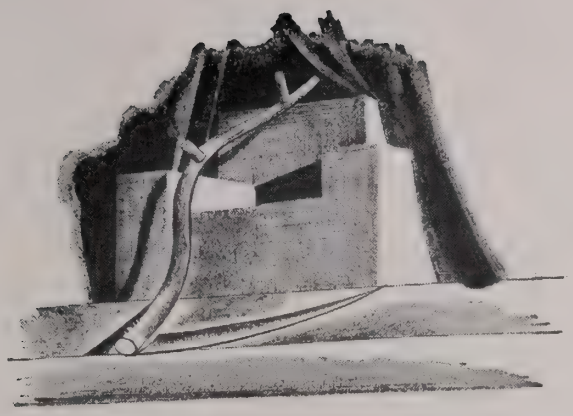
Disease as Reprisal II

Why was Jehoram smitten with a bowel disease?
He had committed acts that were evil in the eyes of the Lord.
And after all this the Lord smote him in his bowels with an incurable disease.
And it came to pass, that in process of time, after the end of two years, his bowels fell out by reason of his sickness: so he died of sore diseases. (II Chronicles, 21:18, 19)

New Directory

The "1968 Directory of Referral and Rehabilitation Resources," is available to physicians in limited supply without charge. This revision was compiled by W. W. Keenan. It is available by request from:

Mr. G. Dean Miller, Consultant
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In Memoriam

Not dead, but gone before.—Rogers

WILLIAM E. TAYLOR, M.D.

Dr. William Taylor, 43, Minneapolis obstetrician-gynecologist, died February 24. He received his medical degree at the University of Minnesota and had practiced obstetrics and gynecology since 1954.

He was on the staff of St. Mary's, Glenwood Hills and Methodist hospitals and was third vice chairman of the third district DFL. Dr. Taylor was a member of the Hennepin County Medical Society, American Medical Association and the Minnesota State Medical Association.

He is survived by his wife, three sons and three daughters.

FRED J. PRATT, SR. M.D.

Dr. Fred J. Pratt, 91, retired otolaryngologist, died January 17. Born in Jackson, Michigan, Dr. Pratt obtained his medical degree at the University of Michigan.

He was a member of the Minnesota Academy of Ophthalmology and Otolaryngology, the American Medical Association, Hennepin County Medical Society and a 50 Club and Life Member of the Minnesota State Medical Association.

He is survived by his son, Dr. Fred J. Pratt, Jr.

HERBERT H. BUSHER, M.D.

Dr. Herbert H. Busher, 75, St. Paul surgeon, died February 26. He graduated from the University of Minnesota Medical School in 1919 and interned at the University of Minnesota.

Dr. Busher was a member of the American College of Surgery, the Ramsey County Medical Society, the American Medical Association and was a Life Member of the Minnesota State Medical Association. He was to have been accepted as a member of the 50 Club of the Minnesota State Medical Association last month at the Association's Annual Meeting in Rochester.

He is survived by his wife.

NICOLAY H. SCHELDRUP, M.D.

Dr. Nicolay H. Scheldrup, 94, Minneapolis physician for more than thirty years, died April 9 in Miami, Florida. He started his practice in Granite Falls in 1897 after receiving his medical degree at Rush Medical School, Chicago, and in 1907 moved his practice to Minneapolis.

Dr. Scheldrup was a member of the Hennepin County Medical Society and the American Medical Association and a 50 Club and Associate Member of the Minnesota State Medical Association.

He bore the title of Sir having been knighted by the King of Norway for his work with the Norwegians in Minnesota.

He is survived by a daughter and three sons, one of whom is Dr. Eugene W. Scheldrup of Iowa City, Iowa.

GEORGE E. McGEARY, M.D.

Dr. George E. McGeary, 74, Minneapolis physician died May 2, 1967, in Florida. He was born in St. Paul, Minnesota, and obtained his medical degree at the University of Minnesota.

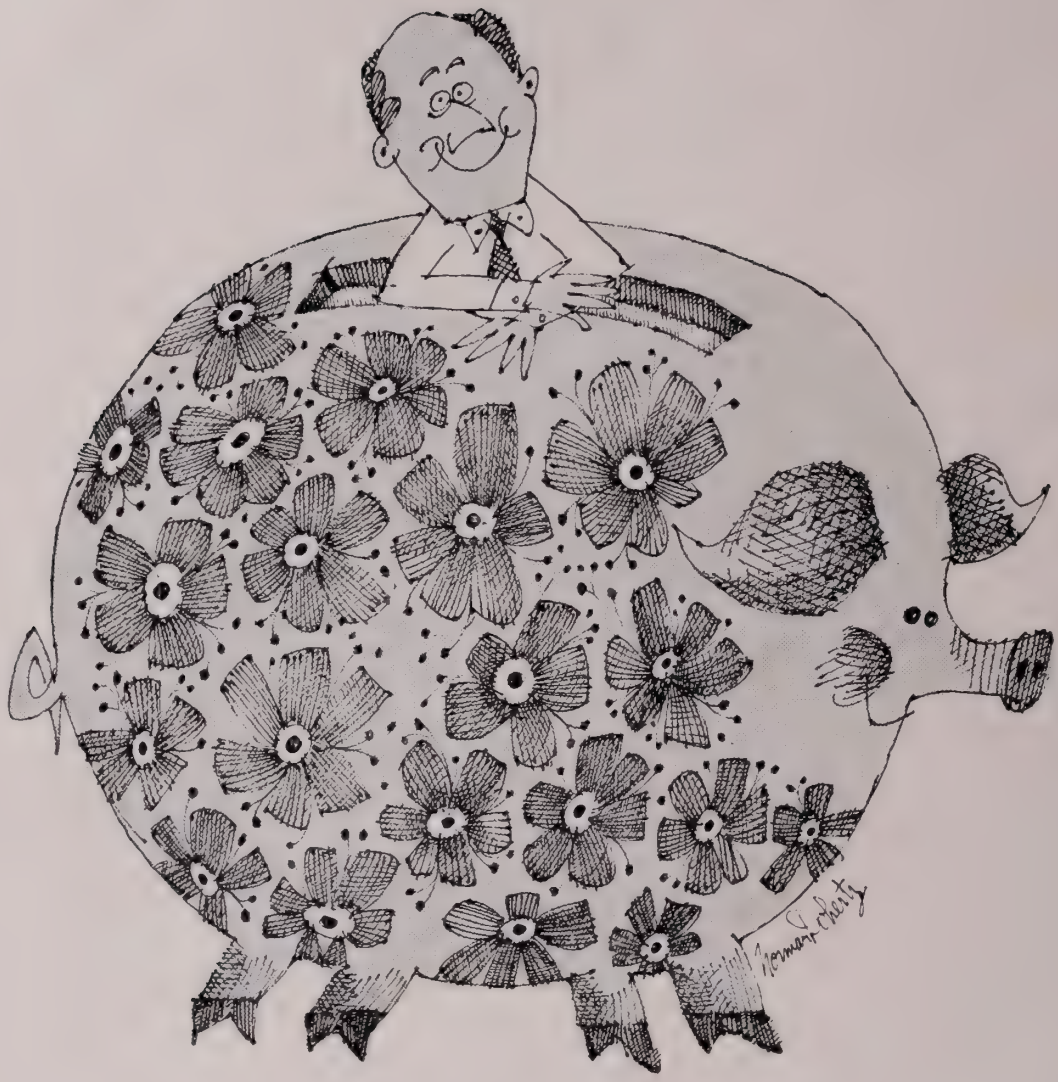
Dr. McGeary was a member of the Hennepin County Medical Society and the American Medical Association and was an Associate Member of the Minnesota State Medical Association.

VIRGIL J. SCHWARTZ, M.D.

Dr. Virgil J. Schwartz, 73, well-known ophthalmologist, died April 17, after a long illness. Dr. Schwartz came to the United States in 1900 and practiced medicine in Minneapolis for over forty years. He was a graduate of the University of Minnesota Medical School, where he served as a teacher of ophthalmology.

He was a member of the American College of Surgeons, the American Academy of Ophthalmology and Otolaryngology, the American Medical Association and the Hennepin County Medical Society. He was also a Life Member of the Minnesota State Medical Association and was honored posthumously as a 50 Club Member during the Association's Annual Meeting in Rochester.

He is survived by his wife and a daughter.

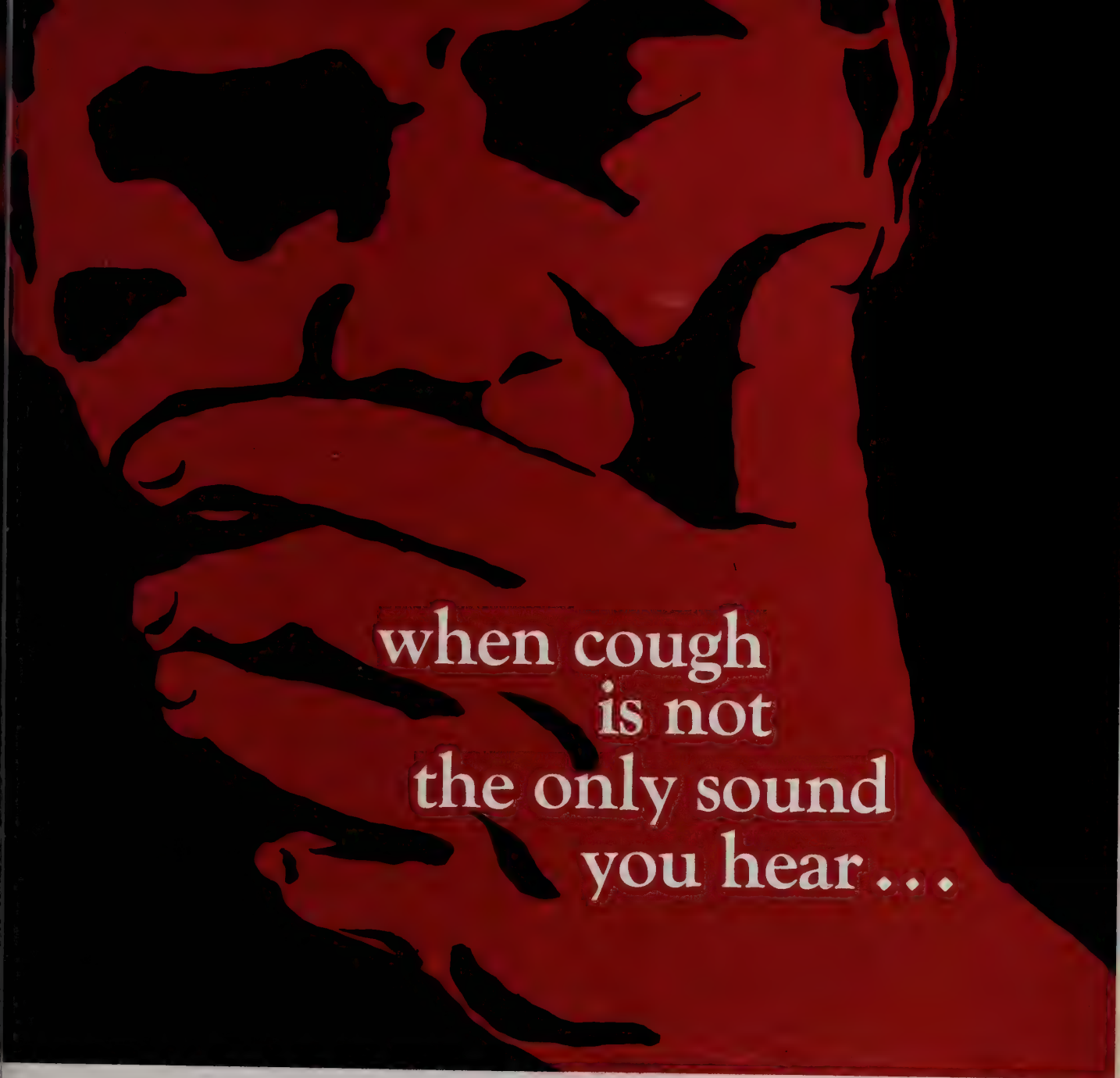


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American Cancer Society

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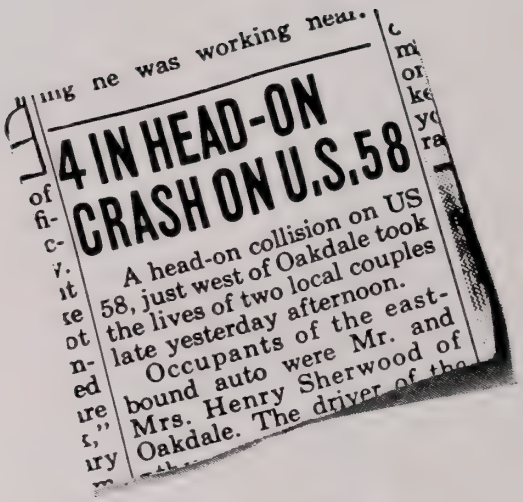
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Meetings and Announcements

A good listener is not only popular everywhere, but after a while he knows something.—Wilson Mizner

JUNE

Nicollet-LeSueur County Medical Society, June 3, Holiday House, 6:30 P.M.

Southwestern Minnesota Medical Society, June 3, Ehlers Supper Club, 7:00 P.M.

Scott-Carver County Medical Society, June 4, New Prague Country Club, 7:30 P.M.

St. Louis County Medical Society Executive Committee, St. Luke's Hospital, June 13, 6:00 P.M.—Regular Meeting, St. Luke's Hospital, 8:00 P.M.

Kandiyohi-Swift-Meeker County Medical Society, June 20, Litchfield Country Club, 5:00 P.M.

McLeod County Medical Society, June 20.

Children's Hospital, Denver, Summer Clinics at Vail, June 26-28. Write: Department of Continuing Education, Children's Hospital, 19th Avenue at Downing, Denver, Colorado.

American College of Preventive Medicine, San Francisco, June 16-20. Exec-Sec: E. A. Piszczek, M.D., 6410 N. Leona Ave., Chicago.

Cardiovascular Seminar (10th Biennial), (Sponsored by Section of Cardiology, University of Miami School of Medicine, Heart Association of Greater Miami, Council of Clinical Cardiology of American Heart Association, Florida State Board of Health, and Florida Heart Association), Doral Country Club, Miami, Fla., June 6-8. Info.: Heart Association of Greater Miami, 5080 Biscayne Blvd., Miami, Florida.

American Society of Radiologic Technologists, Statler-Hilton Hotel, Los Angeles, June 15-20. Exec.-Sec.: Genevieve J. Eilert, 537 S. Main St., Fond du Lac, Wisconsin.

Wisconsin Society of Pathologists (Spring Meeting) Eagle Waters Resort, Eagle River, Wis., June 7-9. Info.: Edwin L. Bemis, M.D., Wisconsin Society of Pathologists, 561 N. 15th St., Milwaukee.

American Medical Association, San Francisco, June 16-20. Exec. Vice Pres.: F. J. L. Blasingame, M.D., 535 N. Dearborn St., Chicago.

American Neurological Association, Washington Hilton, Washington, D.C., June 17-19. Sec.-Treas.: Melvin D. Yahr, M.D., 710 W. 168th St., New York.

JULY

Summer Camp for Diabetic Children, July 14 through August 4, at Holiday Home, Lake Geneva, Wisconsin. Applications may be obtained from: Diabetes Association, 620 North Michigan Avenue, Chicago.

Postgraduate Course, Ophthalmology, The Stanley Hotel, Estes Park, Colorado, July 8-11. Contact: University of Colorado School of Medicine, Denver.

Air Pollution Medical Research Conference (Sponsors: Denver Medical Society, Colorado Medical Society, American Thoracic Society, American College of Chest Physicians, Colorado State Dept. of Public Health, U.S. Public Health Service, and American Medical Association), Denver-Hilton Hotel, Denver, July 22-24. Info.: AMA Department of Environmental Health, 535 N. Deaborn St., Chicago.

The Minnesota Thoracic Society and the Minnesota Respiratory Health Association announce a second award contest for medical students, interns and resident physicians in Minnesota.

(A) An award of $200.00 is offered for the best paper submitted by a senior medical student or intern on some aspect of respiratory disease, preferably based upon laboratory or clinical investigation.

(B) An award of $300.00 is offered for the best paper submitted by a resident physician based upon clinical or laboratory investigation in the area of respiratory disease.

Further information may be obtained from the Secretary. Entries should be submitted by September 1, 1968 to: David E. Dines, M.D., Secretary, Minnesota Thoracic Society, Mayo Clinic, Rochester, Minnesota.

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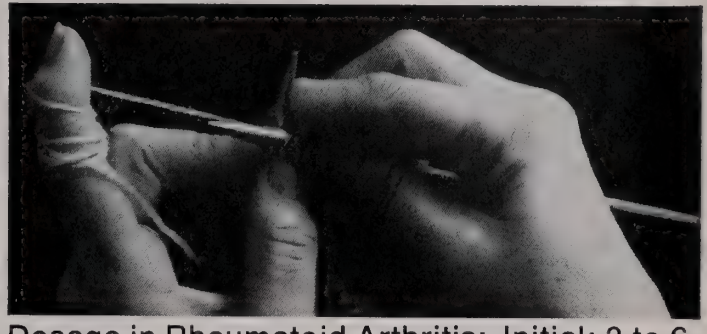
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Contraindications: Edema; danger of cardiac decompensation; history or symptoms of peptic ulcer; renal, hepatic or cardiac damage; history of drug allergy; history of blood dyscrasia. The drug should not be given when the patient is senile or when other potent drugs are given concurrently. Large doses of Butazolidin alka are contraindicated in glaucoma.

Warning: If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Instances of severe bleeding have occurred. Persistent or severe dyspepsia may indicate peptic ulcer; perform upper gastrointestinal x-ray diagnostic tests if drug is continued. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy. Use with caution in the first trimester of pregnancy and in patients with thyroid disease.

Precautions: Before prescribing, carefully select patients, avoiding those responsive to routine measures as well as contraindicated patients. Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patient should not exceed recommended dosage, should be closely supervised and should be warned to discontinue the drug and report immediately if fever, sore throat, or mouth lesions (symptoms of blood dyscrasia); sudden weight gain (water retention); skin reactions; black or tarry stools or other evidence of intestinal hemorrhage occur. Make complete blood counts at weekly intervals during early therapy and at 2-week intervals thereafter. Discontinue the drug immediately and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.

Adverse Reactions: The more common are nausea and edema. Swelling of the ankles or face may be minimized by withholding dietary salt, reduction in dosage or use of diuretics. In elderly patients and in those with hypertension the drug should be discontinued with the appearance of edema. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. The patient should be instructed to take doses immediately before or after meals or with milk to minimize gastric upset. Drug rash occasionally occurs. If it does, promptly discontinue the drug. Agranulocytosis, exfoliative dermatitis, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), or a generalized allergic reaction similar to serum sickness may occur and require permanent withdrawal of medication. Agranulocytosis can occur suddenly in spite of regular, repeated normal white counts. Stomatitis, salivary gland enlargement, vomiting, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported. While not definitely attributable to the drug, a causal relationship cannot be excluded. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, hypersensitivity angiitis, pericarditis and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.



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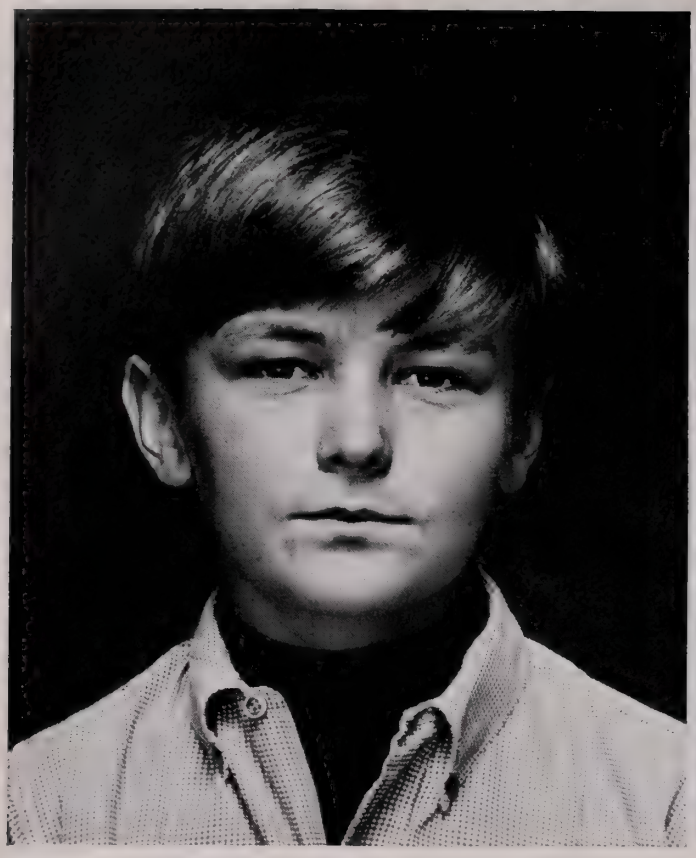
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History of Medicine

Memories of 30 Years of Group Experience in Anesthesia*

JOHN S. LUNDY, M.D.
Seattle, Washington

I HAVE CHOSEN the title of this talk because I know of no better way for the ready, authoritative and usually pleasant acquisition of extensive knowledge than exposure to the experience of a group of colleagues and fellow workers. Each member of a group such as this contributes, in theory at least, at the same time that he is benefitting from the experience of every other member. In the absence of such a group within one's specialty, one would have to find a substitute in the form of meetings of state, regional or national meetings of a general nature, and that can be pretty poor fare.

I can well remember the paucity of group experience and agencies for the exchange of knowledge in anesthesia, because I started entirely alone in this field and, perforce, developed the group here and other groups elsewhere. Then, when I retired from service at the Mayo Clinic in 1959, I returned to private practice alone.

The Boy Anesthesiologist

I must have had some sort of predestination for the specialty of anesthesiology, or perhaps a genial diathesis toward it, because my first memory of it goes back to 1910, when I visited a dental clinic in Grand Forks, North Dakota, in the course of which the late Dr. J. A. Heidbrink, of Minneapolis, was demonstrating his new invention, the gas machine. A boy of 16 years, I watched him anesthetize a man in a dental chair on the stage of a theater and extract some teeth. When the man awoke he laughed interminably. I said to myself, "He must have given him 'laughing gas.'" That was indeed what Dr. Heidbrink had administered: nitrous oxide and oxygen. I remember how impressed I was.

My father was a pioneer of the American frontier, but I never knew him. He had obtained license No. 55 in the Territory of Dakota, in 1885,[1,2] but died of pneumonia at the age of 35 years when I was 18 months old. The physicians who followed him in practice in Inkster, North Dakota, took a benign and protective interest in me and encouraged me to follow medicine and the doings of physicians in the vicinity. And so I began to give anesthetic agents for a Dr. B. D. Lemery, who had been encouraged to become a physician by my father. He instructed me in the necessity for maintenance of a patent airway, and taught me how to administer the ACE mixture, which was one part alcohol, two parts chloroform, and three parts ether, all together in one bottle.

I never forgot this early experience, and it was recalled to me vividly when two relatively noninflammable general anesthetic agents, Fluothane (halothane) and Penthrane (methoxyflurone), were recently introduced into practice. Memory enabled me to visualize what would have been the delight of the originator of the ACE mixture had he been able to use these two agents supplied in separate containers on a gas machine. As for myself, I have derived much satisfaction from the use of these two agents alone, combined, and with nitrous oxide and oxygen on numerous occasions. I have been able thereby to establish a state of anesthesia which has seemed to me to be more satisfactory than any that I have been able to produce in the past with the general anesthetic agents then available.

*Read before the First Group Meeting of the Section of Anesthesiology of the Mayo Clinic and Mayo Foundation, Rochester, Minnesota, October 28, 1967.

Anesthesia In and Out of School

I administered anesthetic agents for my friend, Dr. Lemery, until I was graduated from the University of North Dakota in 1917. I then entered Rush Medical College. I lived in the Alpha Kappa Kappa fraternity house on the west side of Chicago. My roommate, Dr. Proctor C. Waldo, and I carried out anesthesia in the Presbyterian Hospital in Chicago on a number of occasions for such well-known men as the father of Dr. Evarts A. Graham, for Dr. Arthur Dean Bevan, and for many others, so that after my graduation from medical school, during an internship at the Harper Hospital in Detroit, I was administering anesthetic agents because I was the only one of the group of interns who knew how to manage a gas machine. It was at that hospital that I had my first experience with nurse anesthetists. The department was headed by Dr. James Shannon, a dentist, who understandably stopped his work in anesthesiology shortly after he invented a new clutch for the Cadillac automobile.

Seattle Days: Early Lessons

After my internship I visited the West, which brought me in the fall of 1920 to Seattle, Washington. There I opened an office in the Joshua Green Building. As luck would have it, at the moment I was signing the lease for space in another physician's suite, he asked me if I could give an anesthetic agent. I told him that was the one thing I knew I could do, and he engaged me for the next morning, in Columbus Hospital, in Seattle. Thus I began the practice of medicine for myself, at the first hour of the first day, by giving a general anesthetic agent.

About a year later another man and I attended a convention of the Pacific Coast Association of Anesthetists in Portland, Oregon. The group consisted of six or seven women physicians and two male physicians. We have come a long way from this infinitesimal beginning in Seattle. Now several groups of men associated in anesthesia would be well able to outnumber the little band of tyro anesthesiologists who attended that old-time meeting in Portland.

At the time I began to practice in Seattle one man there, Dr. Louis Maxson, devoted full time to general anesthesia. I made sure that I did not interfere with his clientele, and within a short time I had built up a practice which more than kept me busy. In all cases I kept a record, in duplicate, of the blood pressure, pulse rate, and the rate of respiration.

This type of record-keeping was something new at the time and was greatly admired by the surgeons with whom I worked. It was not long before I found myself with more appointments than I could manage personally, and so I gradually arranged for the services of five men to accommodate my overflow of calls.

I was fortunate enough to be able to devise a plan which proved to be much more successful for all concerned than any arrangement which I have seen or heard of since. Since all calls from surgeons for our services came into my office, they were received by my two office girls, who thereupon tried to complete my schedule for each day. Should it happen that six calls came in for an anesthesia session at 8:00 in the morning on the same day, the result was that each of us was given an assignment. In such an event I of course had nothing to do with the sessions conducted by the others unless a surgeon complained to me that the management of anesthesia for his patient had not conformed to the standards which I had set up for anesthesia in general. I then would call the man who had been in charge of the anesthesia and explain to him that the surgeon had not been satisfied because the session had not been managed according to the standards I was known to use. I would then caution him that if he wished more calls to be referred to him from my office, he would have to conform to my standards of general anesthesia. Such an admonition was sufficient to correct the situation. It was the only hint of a disciplinary measure that was required.

The group practice of anesthesia never fails to be interesting and sometimes lively, but it is possible for the anesthesiologist to be destroyed by his own success. Suppose a man establishes a practice of anesthesiology which becomes so extensive that he must take on partners. To the partners he gives a vote. As soon as he has taken on two associates, he jeopardizes his management of the group, because his voting partners outnumber him. I believe that success is no accident, which means that a manager

is required to see that a group succeeds. One of the most successful medical managements known to me is that instituted by the two Mayo brothers, who governed their institution with firmness, wisdom, justice and, inevitably, notable success.

In my early days at the Mayo Clinic it was the Mayo brothers who decided what would be done. Other members of the staff had votes, in management, but they had better sense than to use them contrary to the wishes or decisions of the Doctors Mayo. I believe that in private groups engaged in anesthesia someone must be at the helm, even if the place of power has to be rotated over the years until one person is found who has a natural ability for successful management. And the salient advantage of experience in such a group emerges in the fact that one man very quickly learns what will succeed and what will fail, and if he is patient and considerate, yet resourceful, he can lead the group along the pathways to success.

Any small group benefits much from an arrangement whereby, usually each year, one member attends meetings of societies away from home and brings back such information as he can obtain for the good of the whole group.

It is wise, I think, to make some provision within a group for continuity of the performance of certain procedures devised by some associate of recognized ability, so that if that person leaves the group, the techniques he originated will not languish. This counsel applies to large groups as well as small ones. I well recall that toward the end of my tenure at the Mayo Clinic I was developing a certain technique for nerve destruction with an insulated needle emplaced by roentgen-ray control. But scarcely anyone else in my group was interested in what I was doing, so that after I left I noticed that some patients followed me elsewhere, because the technique I had used was no longer available at the Mayo Clinic. This was discouraging to me, but the situation still obtains, and a few patients still come to me from far away to seek medical counsel.

The Chief Speaks: Dr. William J. Mayo

In the few years that I was in Seattle when I began to practice anesthesiology I was active in the King County Medical Society. Finally I was appointed editor of the bulletin of that society and increased the number of pages from four to 32, paying expenses by means of advertisements. As a result of this effort I was elected secretary of the King County Medical Society shortly before I left Seattle in 1924. On the night of the election and annual banquet for the retiring president, it happened that Dr. William J. Mayo, who was on his way to Australia and New Zealand, was a guest speaker. As secretary of the society I was seated next to him on the platform, and we talked about ethylene anesthesia. It was clear that this type of anesthesia was not in use at the Mayo Clinic. He asked me to walk to the railway station with him after the meeting, and just as he left for his train to Vancouver he invited me to come to the Mayo Clinic.[3] I did so. In 1923 I had administered ethylene as a general anesthetic agent for the first time to infants who had pyloric spasm. The patients did very well. I reported the series the next year.[4]

I also had administered ethylene for one or two operations on the gallbladder in Portland, Oregon, for the late Dr. Thomas Joyce. In 1966 I arranged an exhibit at the annual meeting of the Washington State Medical Association on blood transfusion, blood banking, and the early history of ethylene anesthesia in the Pacific Northwest, some of the material emerging from the early experiences of which I speak.

At the Mayo Clinic: 1924

Soon after my arrival in Rochester, Minnesota, in March, 1924, I could see that in all likelihood the Mayo Clinic would continue to enlarge impressively, which meant that concomitantly the field of anesthesia within the Clinic would be much expanded indeed, as the years went by. I decided that I would try to make one contribution to anesthesiology for each of the 35 years which lay ahead of me. On the basis of experience in the country and on farms I realized that one must plant several crops if one expects to have one real harvest each year. Hence, I tried to keep five projects in anesthesia going all the time, hoping for one good harvest each year while I was here.

Early Graduate Training

During my early years at the Mayo Clinic it

was the general understanding of all concerned that each fellow, or graduate student, enrolled in the Mayo Graduate School of Medicine, would attempt to obtain an advanced degree in his special field from the University of Minnesota. I supported and encouraged this plan as soon as I was able to establish graduate fellowships in anesthesiology. Each of the fellows in anesthesiology who sought a master's degree succeeded, for the most part. Each fellow, as he assumed his fellowship, was given an individual identifying number. I believe this practice is still followed. Since the autonomy of the American Board of Anesthesiology, Inc., was established in 1941, I am not sure that all fellows of the Mayo Graduate School of Medicine still seek an advanced degree from the University of Minnesota, because they are more concerned, practically, with certification by this board than they are in acquisition of an advanced degree. Yet I believe it is of permanent value and significant of achievement within one's field to be able to append the designations of advanced degrees after one's name. I can say this with complete equanimity, because I do not have any advanced degrees other than honorary ones. I have had to make my way without such prestigious insignia.

Subspecialties in Anesthesiology

I had a plan for the formation of a section devoted to anesthesiology as soon as Dr. Charles F. McCuskey joined me at the Mayo Clinic in 1925. His coming meant that we could provide a certain degree of clinical service in anesthesia to hospitals in which surgeons, obstetricians and dentists of the Mayo Clinic worked. Thereafter, consultants were added to the section which I organized, and I tried to designate a particular field in anesthesiology to which each one could devote the major part of his interest outside his clinical responsibilities. For example, Dr. Ralph M. Tovell became an authority on anesthesia records, so that data could be obtained readily and accurately for study and reports. Dr. E. B. Tuohy covered general physiology, Dr. L. H. Mousel covered the area of the chest, Dr. R. Charles Adams wrote his book on intravenous anesthesia, Dr. T. H. Seldon covered blood transfusion and conducted the new blood bank, and Dr. John A. Paulson supervised the nurse anesthetists. These are a few illustrations. Also, for some 28 years I prepared an annual report of the Section of Anesthesiology, not only for publication in the *Proceedings of the Staff Meetings of the Mayo Clinic*, but for submission *in extenso* to the Board of Governors as well. The latter version was a separate and more detailed account. I have seen no such annual reports from that section recently.

The First Laboratory of Anatomy

By 1927 it became apparent to me that my colleagues and I needed more anatomical knowledge, and I therefore brought about the establishment of a laboratory of anatomy. This I maintained for 20 years without outside help, until I found it was essential that a full-time anatomist be obtained. I persuaded the Board of Governors to secure one: since 1947 the services of a Section of Anatomy headed by an outstanding anatomist have been available to members of the staff.

Blood Transfusion and Blood Bank

In 1933 Dr. C. H. Mayo decided that someone should be directed to take charge of the transfusion of blood to infants, and I was selected. In 1934 I was asked to supervise all work in transfusion.

In 1935 Dr. William Carpenter MacCarty, of Saint Mary's Hospital, allowed me to store citrated blood for transfusion in his laboratory refrigerators at the hospital, and thus was established the first blood bank in North America, as far as I can find out. The Cook County Hospital in Chicago began such a service the next year, in 1936. This incident can be validated, because I reported the establishment of my blood bank in my annual report[5] for 1935. It is thus incontestable that the first blood bank was set up in Rochester at Saint Mary's Hospital.

Anesthesia Abstracts

By 1937 it seemed to me that we ought to have a journal club in the Section of Anesthesiology. I organized one, and assigned papers in the literature to be read by each member of the section, and to be reported on at a meeting of the club. Some of the less intrepid members of the group could not overcome their diffidence sufficiently to make an oral presenta-

tion of what they had read, but since they had prepared these reports and the reports had been typed, it occurred to me that somehow we ought to see that they were published. Such was the inception of what later became *Anesthesia Abstracts,* a successful venture which persisted for some time. Soon Miss Florence A. McQuillen, C.R.N.A., of Chicago, took over all the work involved in the preparation of material for this publication, and she alone produced *Anesthesia Abstracts* from then until 1965, when she finally abandoned the effort, much to my regret.

Anesthesiologists vs. Nurse Anesthetists

During my earliest years at the Mayo Clinic the only recognized national organization devoted to anesthesia was the International Anesthesia Research Society. It was then headed by Dr. Frank H. McMechan, who was so crippled by arthritis that he was more or less helpless,[6] but as a consequence of the great efforts of his wife, Laurette, he was able to carry on his responsibilities. He was determined that anesthetic agents would be administered only by those who held either a medical or a dental degree. This attitude caused a considerable difference of opinion among those of us who recognized the great contributions which nurses had made in administering anesthetic agents prior to the time that physicians like myself had entered the field. The late Dr. Arthur Dean Bevan, of Chicago, head of the Department of Surgery in the Rush Medical College and president of the American Medical Association in 1918 and 1919, had a novel idea which he defended stoutly: he maintained that the proper person to administer general anesthetic agents was a woman doctor of medicine.

It was apparent to me, even then, that it was expedient to use any well-trained and experienced person who was available to give anesthetic agents. As a matter of fact, in the early days after the invention of the gas machine, lay persons acting as salesmen for the manufacturing company in question administered anesthetic agents in the demonstration of their gas machines, and they were much better qualified for that purpose than anyone else at that time. As it is now, recent emphasis upon the necessity of using paramedical personnel as much as possible in the practice of clinical medicine as a means of enhancing the effectiveness of the physician only points up the wisdom of our use of nurse anesthetists in years gone by.

Section on Anesthesiology, American Medical Association

In those early years I felt as if I were garbed in Joseph's coat of many colors. I was anxious to join some organization in which a physician like myself, with my primary interest in everything pertaining to anesthesia, might take part in a relationship which would be of mutual benefit to society, to physicians and surgeons and especially to patients. I therefore applied to the American College of Surgeons, since every member of that organization had a basic concern with anesthesia. But the College refused to consider me for membership because I was not a surgeon. I then applied to the American College of Physicians, which straightaway gave me the same reception. I thus remained suspended in a medical limbo, and I often maintained that I was in fact the last person the patient ever saw between the attending physician or surgeon and the undertaker. But, since I never became known for indecision or abnegation, I set about to hot up the fire and see what rare distillation I could brew. It was evident that we in anesthesia would have to have our own working organization. For that reason, every time I passed through Chicago, which was often, I would call upon the late Dr. Olin West, secretary and general manager of the American Medical Association from 1924 to 1946, and urge him to create a section on anesthesia within the American Medical Association. As the years went by I had my way. The Section on Anesthesiology was established in 1940,[7] with the implicit understanding that I was to remain secretary until the section should have become well functioning. That I did for 17 years.

International Anesthesia Research Society

At about that time I was asked to make a decision by a friend of mine who said that as the result of a variety of circumstances he was in a position either to sustain or to destroy the old organization of anesthetists which Dr. Frank H. McMechan had largely built up and

maintained. I urged my friend to take measures which would perpetuate the society in question, saying that I thought scientific competition carried on in two organizations—the American Society of Anesthetists, Inc., as it was then known, and the older International Anesthesia Research Society—would be a good thing. I think I was justified in that opinion, particularly since in recent years Dr. T. Harry Seldon, a member of the Section of Anesthesiology of the Mayo Clinic, has helped to make the International Anesthesia Research Society very successful. He has been a member of the board of trustees of the society since 1948 and editor of its journal, *Anesthesia and Analgesia —Current Researches*, since 1954.

American Society of Anesthesiologists, Inc.

Some time in the 1930's I had lunch with Dr. Paul M. Wood, of New York City, in the course of which I told him I thought that as physicians administering anesthetic agents we ought to have a name which would distinguish us from the nurse anesthetists, who had organized the National Association of Nurse Anesthetists in 1931.* He proposed the word, "anesthesiology." I told him to look into the subject carefully, which he did. Later we discussed it again and decided that the word was valid etymologically. I said: "Let's put it to work."

Among other things, we talked about creation of a national society. It was agreed that he would try to get the New York Society of Anesthetists, which had existed since 1905, to change its name to the "American Society of Anesthetists, Inc.," which was done in 1935. It was not until 1945, however, that we were able to substitute the word, "anesthesiologists," for "anesthetists." In the meantime we had managed to establish a journal, the first issue of which appeared in July, 1940, designated by our new word, *Anesthesiology*. The title of the journal immediately established the name, "anesthesiology," in every medical library, and since custom is ineluctably more binding than fiat, the name of our journal became accepted everywhere, as did the variant, "anesthesiologist."

*This organization changed its name to the present "American Association of Nurse Anesthetists" in 1939.

American Board of Anesthesiology, Inc.

Shortly before *Anesthesiology* was founded, the various certifying boards in medicine and surgery were being formed. It seemed desirable that there be a board to certify specialists in anesthesia. Again Paul Wood and I discussed how such a board might be created. It was our conviction that we could organize a college of anesthesiologists within the American Society of Anesthetists, Inc., for the examination and certification of competent physicians engaged in the practice of anesthesia. Such was our plan at the moment, but it did not turn out that way. Before we could make much progress with plans for a college of anesthesiologists a number of persons, and especially the late Dr. Ralph Tovell, concluded an arrangement with Dr. Fred W. Rankin, at the time secretary of the Section on Surgery of the American Medical Association. A committee of representatives of the American Society of Anesthetists, Inc.; the American Society of Regional Anesthesia, Inc.; and the Section on Surgery of which Dr. Rankin was Secretary, devised a plan for bringing a certifying board in anesthesiology into existence in 1937, as an affiliate of the American Board of Surgery, Inc.[8] It became a separate entity, with the name, "American Board of Anesthesiology, Inc.," in 1941.

American College of Anesthesiologists

However, there was a place for both a college of anesthesiologists and a specialty board, since the board certified only those physicians who limited their practice entirely to anesthesiology, whereas, as we conceived a college of anesthesiologists, it would be empowered to certify a physician as competent in anesthesiology even though he spent but a part of his time in that special field. We pursued our plans, therefore, and the American College of Anesthesiologists was founded in 1947, as a part of the American Society of Anesthesiologists, Inc.

Graduate Refresher Courses

Now it was very apparent during examinations for entrance into the American College of Anesthesiologists that prospective members

were not very well informed on a good number of subjects in medicine. We saw the necessity for some means by which educational endeavors might be carried on. My ideas on the problem and its solution were very definite because I had been participating in the educational program which the American Academy of Opthalmology and Otolaryngology presented each year at annual meetings of the organization. The Academy was offering refresher courses in ophthalmology and otolaryngology which I thought were excellent.

I finally persuaded the American Society of Anesthesiologists, Inc., to pay the expenses of Dr. Stevens J. Martin, of Hartford, Connecticut, president of the Society in 1953, for a trip to Chicago so that he could meet me at one of the meetings of the American Academy of Ophthalmology and Otolaryngology. He did so, and was impressed by what he saw and heard. The next year, under his direction and mine, we began to present refresher courses in anesthesiology and allied subjects at the annual meetings of the American Society of Anesthesiologists, Inc., and my impression is that this educational program has been very successful.

Anesthesia in Europe

In 1938 the Mayo Clinic sent me to Europe with Mrs. Lundy. I visited most of the great medical centers on the continent and in Great Britain, and what I saw there convinced me that anesthesia had made more progress in the United States than anywhere else. This was not sufficient, however, to diminish my lifelong belief that the struggle for improvement in any field must be incessant and vigorous.

Meetings of Societies

The possibilities for the acquisition of valuable knowledge by attendance at medical and scientific meetings are so great that any man privileged to make such journeys is fortunate indeed. I have calculated that the Mayo Clinic through the years allowed me to attend so many meetings and to go on so many clinical trips that the time thus spent amounted to almost three or four months in each year for 30 years. Very likely, in these times, such protracted absences from daily practice would not be tolerated; in fact they probably would not be needed today.

Special Society for Group Anesthesiology

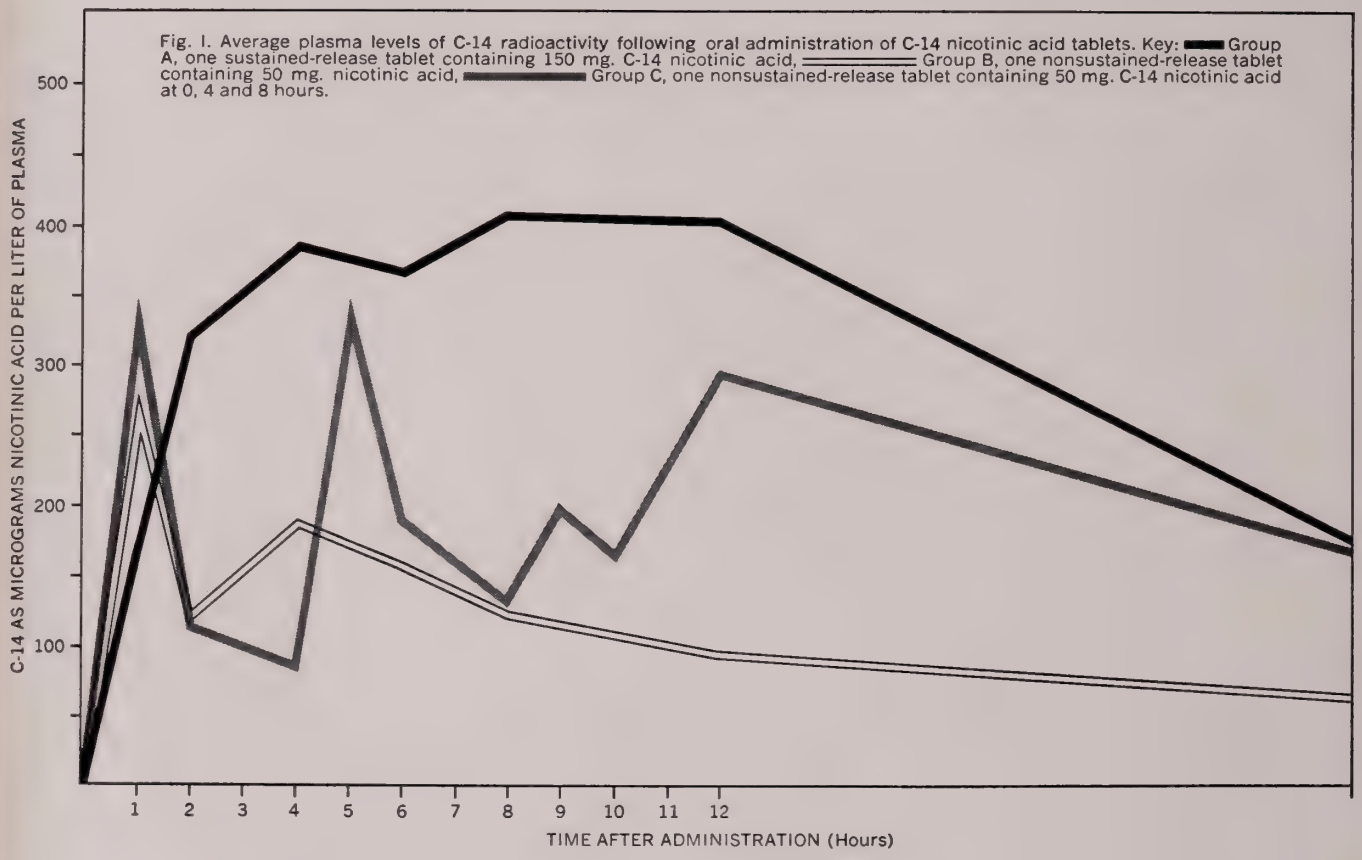
When I contemplate the nature and functions of group experience in anesthesia as a vista encompassing more than a quarter of a century, I am impressed by the fact that the survival and flourishing of this type of group endeavor constitute the best evidence that was needed, and that, when I took up this form of practice in 1924, it was the right thing to do. The number of physicians engaged in this special field of anesthesiology is increasing constantly, and so it is indeed appropriate that such a group as this one—all members of which are interested and most of whom are involved in the group practice of anesthesiology—should be formed. Such an idea in fact was suggested to me many years ago, at a time when there were very few of us in group practice. I rejected it then on the ground that the specialty of anesthesiology ought not to be divided any more extensively than it was at that time, an era in which there were really too few of us. Now the opposite situation exists: there are so many anesthesiologists that small groups within the specialty are necessary.

In a group such as this one I think a practice once employed by the old Anesthetists' Travel Club, founded in 1929, would be desirable to use now. It was the policy of the Anesthetist's Travel Club to invite persons from any specialty to attend the meetings under some form of invitation so long as the front rows were reserved for the original members of the club. I think it would be especially interesting, for instance, to have present men who had been trained by still others who had taken their graduate training in anesthesiology at the Mayo Clinic and the Mayo Graduate School of Medicine. It should prove to be fruitful, also, to invite any who are interested in the field to be present at such meetings. To ensure honesty of purpose there should be no closed-door sessions.

References may be secured from the author.

We meet people who seem to overlook and read us with a smile, but they do not tell us what they read.—Emerson

Sustained circulatory, respiratory and cerebral stimulation for the





(fewer absent doses by absent-minded patients)

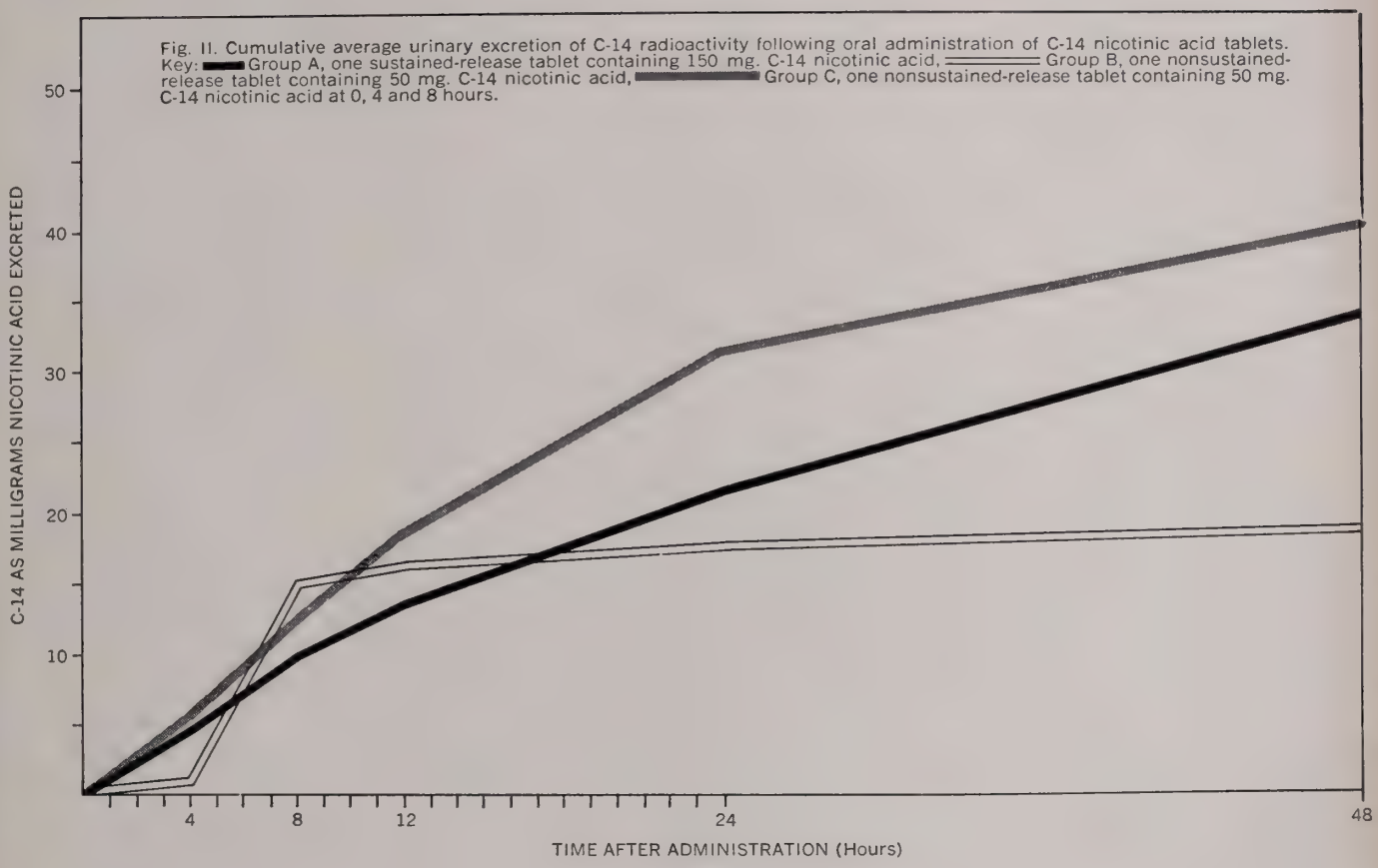
Human volunteer subjects were administered Geroniazol TT tablets with the nicotinic acid component made radioactive with C-14. Plasma and urine samples were analyzed. (See Figures I and II) The radioactive tracer study substantiated the previous clinical evidence that the release of nicotinic acid from the Geroniazol TT tablet produced a gradual rise in plasma levels to a plateau for a total of 12 hours and more.

Such proven sustained activity makes the management of geriatric patients much easier by minimizing the possibility of neglected doses through absent-mindedness or senile confusion. Therapy *can* be continuous on a daily dose of only one Geroniazol TT tablet every 12 hours.

The gradual release of nicotinic acid in Geroniazol TT will provide the well-known peripheral vasodilatation needed in patients with deficient circulation and with a minimum amount (if any) of "flushing." Also, cerebrovascular circulation is complemented by pentylenetetrazol, long-established as a cerebral and respiratory stimulant.

Geroniazol TT improves the typical, unfortunate, signs of senile confusion. Patients become more alert,

aged and debilitated



less confused and moody. Personal care, memory, emotional stability, social attention improve. Fatigue, apathy and irritability are reduced.

A prescription for 100 tablets of Geroniazol TT will permit your patients to enjoy the benefits of time-prolonged nicotinic acid/pentylenetetrazol therapy, at an economical price. Dosage is only one tablet every 12 hours.

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Precautions: Exercise caution when treating patients with a low convulsive threshold.

Side Effects: Side effects are rarely encountered, however due to the vasodilatation effect of nicotinic acid, transitory mild nausea, flushing, tingling and pruritus are possible.

Dosage: One tablet every 12 hours.

Supplied: Prescribe bottles of 100 tablets, to take advantage of recent price reduction.

References: 1. Report by Nuclear Science & Engineering Corp., Pittsburgh, Pa., in files of Philips Roxane Laboratories. 2. Connolly, R.: W. Virginia Med. J. *56*:263 (Aug.) 1960. 3. Curran, T. R., and Phelps, D. K.: Am. Pract. & Digest Treat. *11*:617 (July) 1960.

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Minnesota State Medical Association

Rural Medical Scholarship Winner

As a teenager, Larry Eugene Lyon, winner of the 1967-68 Rural Medical Scholarship, had a serious nasal problem. He was referred for a delicate operation which only a few doctors in the world were qualified to perform. He remembers how lucky and how thankful he felt to have his problem corrected. While a patient he began to think of what a rewarding career he could find in medicine.

Larry is today a freshman medical student at the University of Minnesota Medical School. As the winner of the Rural Medical Scholarship, he will receive $1,000 a year for each of the four years he is in medical school, with the stipulation that he will practice medicine for five years in a rural Minnesota community approved by the Scholarship and Loans Committee immediately after internship. But this is Larry's desire. He was raised in small communities and wants to return to them to assume "what I feel is my responsibility to society and myself."

Larry is the son of Reverend D. F. Lyon and Mrs. Helen Lyon. Rev. Lyon is a Methodist minister in Luverne, Minnesota. Larry was born in Marion, Ohio, but eventually his family moved to Sleepy Eye, Minnesota. After graduating from Sleepy Eye Public High School, he attended and graduated magna cum laude from Hamline University in St. Paul. He married the former Linda Holland and they are expecting their first child this spring.

Larry is the 17th winner of the scholarship established to provide worthy and outstanding students with financial assistance and to insure a continuing supply of physicians for the non-metropolitan areas of Minnesota.



Larry E. Lyon

New drugs take exams, too.

Today, virtually every medical school in the United States cooperates with pharmaceutical manufacturers in the clinical evaluation of new and promising drugs. Just as you might find it significantly more difficult to practice medicine without the useful new compounds made available through original pharmaceutical research in the past twenty years—prescription-drug manufacturers would find it equally difficult to obtain extensive, long-term, dependable evaluations of new therapeutic agents without the close cooperation of medical staffs and clinical facilities of medical schools and teaching hospitals. Such cooperation leads toward more effective care of more patients—the common goal of medical and pharmaceutical research—toward reduction in the cost of disease, toward increase in useful longevity.

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NORTHLANDS REGIONAL MEDICAL PROGRAM

REGIONAL PROGRAM FOR HEART DISEASE, CANCER AND STROKE

New Systems Are Coming in Medicine

In the last six years the following six significant national commission or committee reports suggest patterns for the future in medical education and practice.

I. *Lifetime Learning for Physicians.* This "Dryer Report" published in 1962, recommended an elaborate new system for lifetime learning of physicians in the "University Without Walls." The new coordinated system prescribed cooperative programs between physicians, teaching centers, community hospitals and the medical organization. Continuing education courses must emphasize the following criteria—personal satisfaction, freedom of choice, continuity, accessibility and convenience.

II. *The Graduate Education of Physicians.* Acclamation of this "Millis Report" compares with the epic "Flexner Report" of 1910. "Medicine exists to serve society . . . it must be responsive to the needs of the society it serves." "Physicians are the persons who best know the limitations, the possibilities and the expected directions of change in medical practice, and this fact imposes upon them the obligation of deciding how the health needs of society can best be met." The recommended new national system for control of all graduate medical education included a new medical specialist—the "Primary Physician."

III. *A National Program to Conquer Heart Disease, Cancer and Stroke.* The "DeBakey Report" published in 1964 was the forerunner of the Regional Medical Program Act of 1965. Organized medicine significantly influenced the final form of this legislation and a majority of its recommendations were adopted. This focus is on the patient. The key is local autonomous development of new cooperative arrangements between medical centers and all medical care facilities and personnel.

IV. *Health is a Community Affair.* A National Commission on Community Health Services published a comprehensive report in 1966 after four years of extensive studies. Key recommendations from these studies can be recognized in the Regional Medical Program and Comprehensive Health Planning legislation. The emphasis is on local "action-planning" by community health-planning councils, and geographic definition by "Health Services Marketing Areas."

V. *Meeting the Challenge of Family Practice.* This "Willard Report" by the AMA in 1966 recommends a new system for producing a new specialist

in medicine—the Family Practice Specialist. The family physician is the first medical contact for patients, the key to the referral process, and the integrator of health services. He will be trained to function in a new system where he can call upon appropriate specialists, sub-specialists and paramedical associates to assist him.

VI. *Health Manpower.* This 1967 report documents the needs for large increases in the numbers of almost every category of health care workers. Since an adequate increase in numbers cannot be immediately forthcoming, new systems will be required to improve utilization and effectiveness of existing health manpower.

Can there be any doubt that new systems are coming? Is there any doubt that our profession is challenged to lead in developing new systems to solve medical care and medical education problems? A skeptical "wait-and-see" philosophy will worsen the crisis and increase outside influences.

The Northlands Regional Medical Program offers an opportunity to develop new cooperative arrangements for solution of medical care and medical education problems in Minnesota. We need active participation by all Minnesota physicians.

Winston R. Miller, M.D., F.A.C.P.
Program Director

Poropathy

Arthur de Collard turned up in Richmond, Va., and persuaded the legislature in that State, in 1918, to license him to practice poropathy. Arthur claimed to be a cousin of Napoleon and a graduate of several European universities. His diplomas, he said, had all been burned, and he would not answer the simplest question on the elements of medicine and surgery. The bill defined poropathy and manipulative surgery as a new branch of therapeutics. It employs no medicine taken through the stomach and does not employ the knife. Healing and curative agencies and lotions, however, applied directly to the diseased organs and to the nerves controlling those organs, through the pores of the skin and the mucous membrane, which are opened by medical manipulation, immediately reach the disease or ailment through the eliminating organs, and by this process heal and cure most of the ills to which flesh is heir, including: internal cancer, cerebrospinal meningitis, epilepsy, tuberculosis of the joints and heart disease. This system, according to the bill, would adjust, heal and cure broken bones, sprains and dislocations. After a committee substitute for the bill and various amendments to the substitute had been rejected, the bill was passed and Arthur de Collard through it acquired the right to practice poropathy in Virginia. There are now several poropathists in the state who have taken a course under de Collard.*

*Morris Fishbein, M.D.: The New Medical Follies, 1927.

Saffron

Saffron is such a special remedy for those that have consumption of the lungs and are—as we term it—at death's door, and almost past breathing, that it bringeth breath again, and prolongeth life to certain days, if ten or twenty grains at most be given in new or sweet wine, it presently and in a moment, removeth away difficulty of breathing, which most dangerously and suddenly happeneth.—Old Herbal

Horsemint

Horsemint is good for wind and colic in the stomach.—Nicholas Culpeper



Physician's Diary

Dr. John H. Rosenow, a clinical instructor in surgery at the University of Minnesota Medical School, has been appointed Senior Associate Editor of *Modern Medicine.*

* * *

St. Mary's Hospital will have a Extended Care Center by the spring of this year, and **Eitel Hospital** has a new east wing and major renovation work in the 60-year-old south wing.

* * *

Dr. C. A. Tietz of the Lenont-Peterson Clinic in Virginia was recently certified as a diplomate of the American Board of Obstetrics and Gynecology, and **Dr. Patrick Bosley,** Balaton, has been elected to active membership in the American Academy of General Practice.

* * *

Dr. Clarence J. Rowe, St. Paul, has been appointed chairman of the Joint Committee on Mental Health in Industry of the American Medical Association.

* * *

Dr. Joseph H. Pratt, head of a section of surgery in the Mayo Clinic, was elected president of the Society of Pelvic Surgeons at their annual meeting.

* * *

Dr. George B. Logan, Rochester, has been reappointed principal representative of the American Academy of Pediatrics of the American Medical Association's Interspecialty Committee for 1968.

* * *

Dr. Ramon Mendiola has been named Chief of Staff of the Waconia Ridgeview Hospital, and **Dr. Robert T. Hilker** has been elected president and Chief of Staff of the medical staff of the Owatonna City Hospital.

* * *

Dr. Walter Dowswell has retired after twenty-five years of dedicated service in the practice of medicine in Kerkhoven.

* * *

Dr. William H. Rock is the newly elected Chief of the Medical Staff of Mercy Hospital in Anoka, and **Dr. L. G. Reichelt** was elected Chief of Staff of the Wesley Hospital Medical Staff of Wadena.

Dr. Herman E. Drill, Hopkins, has been appointed to a one-year term on the Committee on Indian Health of the American Academy of General Practice.

* * *

Dr. W. Albert Sullivan, Jr., Minneapolis, has been reappointed a member of the Committee on Continuing Medical Education of the American Medical Association.

* * *

Dr. Charles Field, has been named president-elect of the medical staff of the Olmsted Community Hospital. **Dr. Frank Sander** will assume presidency of the hospital.

* * *

Dr. O. E. Winger is the newly elected president of Pierz's St. Gabriel's Hospital Medical Staff, and **Dr. Carl E. Christenson** is the new president of Ortonville's Municipal Hospital Medical Staff.

* * *

Dr. Victor K. Funk of Minnetonka, former Hennepin County Chest Clinic director, is the recipient of the County's Outstanding Community Service Award.

* * *

Dr. Harry J. Smith of Lake Crystal has been elected to the medical staff of Immanuel Hospital Medical Staff in Mankato, and **Dr. Clarence Everhart** has been named pathologist for Glenwood Hills Hospital in Robbinsdale.

* * *

Dr. Earl Dagg, Thief River Falls, is the newly elected president of the Red River Valley Medical Society. Other officers include: **Dr. Owen Holm,** Crookston, vice president; **Dr. H. D. Clapp,** Crookston, secretary-treasurer.

* * *

Dr. Ralph Knight of Minneapolis was one of four men invited to participate in the Wood Library-Museum's "Distinguished Visitors Week," in April. He joined discussions of current Museum projects and helped identify some of the hundreds of pieces of antique equipment which have been donated to the Museum.



The relief received from the first Trocinate 400 mg. tablet is so prompt that the discomfort of diarrhea ceases to be a bother. May be repeated every four hours.

Upon request, a supply of Trocinate 400 mg. with literature will be sent to physicians for their personal use.

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Classified

Replies to advertisements with key numbers should be mailed in care of Minnesota Medicine, 375 Jackson, St. Paul, Minn. 55101.

GENERAL SURGEON, Certified, part or full-time association in multi-specialty clinic. Alfred F. Anderegg, M.D., 645-5851, 2500 Como Ave., St. Paul, Minnesota.

WANTED: GP to join clinic serving population area of 12,000. City has new hospital, new clinic building, two nursing homes, new Jr-Sr high school, new swimming pool, rich farming area in Red River Valley. Fishing and hunting nearby; metropolitan city close by. Salary open and partnership if interested. Write or call Warren Clinic, Warren, Minnesota 742-6231, area code 218.

WANTED: General practitioner, to join two G.P.'s well established in north central Minnesota community, 2200 pop., 65 miles from Twin Cities. Excellent office space with lab and X-ray, just opened new hospital, all facilities. Assistantship or partnership. Considerable surgery and obstetrics. Hunting, fishing, golf club. Great opening for interested G.P. WRITE MINNESOTA MEDICINE—381; 375 Jackson, St. Paul, 55101.

INTERNIST AND GENERAL PRACTITIONER wanted to join a five-man clinic group in Minneapolis. Complete laboratory and X-ray with board roentgenologist. Excellent hospital staff associations. Salary arrangement to start with early partnership. Write: MINNESOTA MEDICINE—289; 375 Jackson, St. Paul, 55101.

PRACTICE FOR SALE: Well established general practice in South Minneapolis serving an excellent community, within easy reach of the finest hospitals in the State. Very reasonable, low overhead. Splendid opportunity for solo or partnership practice. Write: MINNESOTA MEDICINE-397, 375 Jackson St., St. Paul 55101.

WANTED: GENERAL PRACTITIONERS, anesthesiologist, Urologist, Obstetrician, Orthopedist, & Pediatrician needed in growing community of 15,000. Service area 25,000. Present 83 bed general hospital. New 100+ bed automated hospital to be completed within 2 years. City has excellent industry, school system, and recreational activities. 45 minutes from Madison or Milwaukee. Future unusually promising. For more information contact: Administrator, Watertown Memorial Hospital, Watertown, Wis.

NEW DENTAL MEDICAL CLINIC, 5201 Bloomington Avenue South, Minneapolis 55417. Physician space available 1400 square feet. Contact: Dr. Roger K. Schroeder, 824-8957 (office) or 890-4690 (home).

Classified Advertisements

DIRECTOR OF MEDICAL EDUCATION, full time —Methodist Hospital, St. Louis Park, Minnesota 55426. Contact Mr. Earl Dresser, Administrator or Dr. W. John Dawson, acting director of medical education.

THREE MAN group in North West Wisconsin Resort, State Conservation and Retirement Area needs two more physicians adequately to serve their practice. Facilities offered are three-room physician suites, X-ray and lab under AMT technician, RN-only nursing personnel. New accredited thirty-two bed hospital and forty-six bed nursing home. Deer and duck hunting, fishing within five minutes of town. Internist most needed; generalists welcomed. Will meet any reasonable salary request. Partnership after one year. Write: MINNESOTA MEDICINE—365; 375 Jackson St., St. Paul 55101.

GENERAL PRACTITIONER wanted to join well-established practitioner. New clinic building—90 miles east of St. Paul—city of 14,000. Early partnership with full hospital facilities. Ideal location. L. W. Picotte, M.D.; Chippewa Falls, Wisconsin.

WANTED: YOUNG PHYSICIAN for association leading to partnership with four well-established General Practitioners in fast-growing suburb of St. Paul. Excellent clinic facilities in nearly new, partnership owned, well equipped, medical center building. Contact: A. Eugene Muller, M.D., North St. Paul Medical Center, 2579 East 7th Avenue, North St. Paul, Minnesota 55109.

OPENING IN MT. LAKE, Minnesota for General Practice. Associate practice if desired, adequate vacations, excellent office space, financial help if needed, new 25-bed hospital, nursing home, two old people's homes, over 100-bed capacity in total. Excellent schools and churches. If interested, call collect 427-3515 Mt. Lake, Minnesota or contact Steinle Drug.

PHYSICIAN WANTED: G.P. with G.P. residency or Internal Medicine training or Internist to join two busy G.P.'s in new, fully equipped office 25 miles from downtown Minneapolis, Minnesota. Accredited hospital. Salary open. Prefer military service completed. Write: MINNESOTA MEDICINE-398, 375 Jackson St., St. Paul 55101.

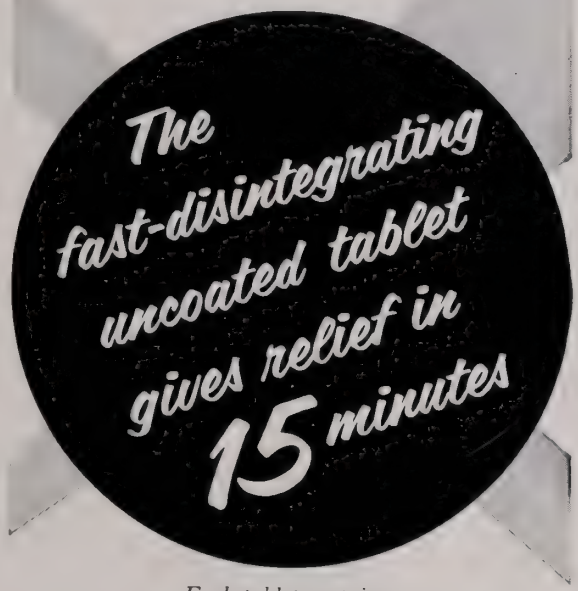
PUBLIC HEALTH PHYSICIAN: To fill immediate vacancies. Salary range $18,729 to $24,430 annually, depending on qualifications. All Michigan civil service benefits. Two positions available: Chief, Pulmonary Disease Section—Supervises all aspects of a statewide program of tuberculosis control; Chief, Section of Preventive Medical Services—Plans, develops, implements, supervises, and evaluates statewide programs in cancer and chronic disease contact. Must possess a master's degree in Public Health and be eligible for a license to practice medicine in Michigan. For additional information contact Dr. John Cowan, Chief Division of Adult Health, Michigan Department of Public Health, Lansing, Michigan. An equal opportunity employer.

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Iodide contraindications: tuberculosis, pregnancy.

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(Continued from page 883)

FOR SALE: Modern clinic building 44 x 80, brick and block construction. Seven years old, adequate examination, emergency treatment and X-ray rooms, plus private offices, and laboratory rooms. Fully air-conditioned. Located in West Central

SEVENTEEN-MAN Wisconsin group located in college community of 40,000 with excellent hospital facilities is seeking additional associated in the following areas: (1) Internal Medicine, (2) Urology, (3) General Surgery and (4) General Practice. For further information please contact D. R. Griffith, M.D., Midelfart Clinic, Eau Claire, Wisconsin 54701.

PSYCHIATRIC RESIDENCIES: Approved three-year progressive program in Metropolitan Detroit area. University associations. Teaching staff of Board men, psychoanalysts, professors, outstanding visiting lecturers. Active Research. Modern physical plant. Salary $8,978; $9,405; $10,213. Five year career program $10,213 to $18,507. 10% increase expected in July. Liberal Civil Service benefits. General Practitioners completed internship four years ago may be eligible for NIMH stipends of $12,000 per year. Write, Director of Education and Research, Northville State Hospital, Northville, Michigan 48167.

SKIING, HUNTING, FISHING and practice of Internal Medicine offered to board qualified or certified internist by 21 man specialty clinic in northern Minnesota. Presently adding new modern facilities to keep up with rapidly expanding economy. Salary first year, shareholder status second year. Reply Russell Anderson, M.D., East Range Clinics, Ltd., Virginia 55792 or call collect, Area Code 218, 741-6244.

WANTED—INTERNIST: Board qualified for four man group in Iowa; two Internists and two Surgeons; own building; Large modern hospital; Midwest shopping and medical center; 30,000; well balanced economy; two hours to three large cities; lake resort 10 miles away; hunting and fishing area; skiing 2 hours away; excellent school system; Junior College; art gallery; superb library facilities. Salary $20,000 to $22,000 depending on qualifications. Early partnership. Write Minnesota Medicine—402, 375 Jackson Street, St. Paul.

RESIDENCIES IN PHYSICAL MEDICINE and Rehabilitation offer challenge and opportunity in a growing field. Comprehensive training utilizing Mayo Clinic facilities and faculty, at $5,400 to $10,000 stipend. Attractive community, excellent school system, cultural advantages. Contact Gordon M. Martin, M.D., Mayo Graduate School of Medicine, Rochester, Minnesota 55901.

OPPORTUNITY FOR CAREER in occupational medicine with large corporation. Multiple locations. Salary plus fringes. Immediate openings in three locations, one in Minnesota. Give rèsumè. Write: MINNESOTA MEDICINE-401, 375 Jackson St., St. Paul 55101.

WANTED: General surgeon, G.P. with G.P. residency or internist to join two very busy general practitioners in new, fully equipped office in Chaska, Minnesota, 25 miles from downtown Minneapolis. Accredited hospital. Salary open. Prefer military service completed. Call collect—612-448-2050 Chaska, Minnesota, Drs. Heinzerling and Pistulka.

FORTY-THREE YEAR old G.P. with extensive general and traumatic surgical experience including orthopedic and cystoscopy. Presently Chief of Staff at hospital. Am considering relocation because of unbearable work load and inability to obtain associate. Present practice grossing $80,000.00. Would consider small group, non-metropolitan area, small community with accredited hospital, general practice with heavy emphasis on surgical interests. Background information, personal and professional with references on request. Write: Minnesota Medicine—404, 375 Jackson, St. Paul 55102.

DeLUXE OFFICE quarters available in downtown area for Doctors, Dentists or optometrists. Start your own practice in busy community. Call or write: M. Bergquist, Cloquet, Minn. 879-9875.

ONAMIA, MINNESOTA, will be needing one or two general practitioners to take over well established practice which will be vacated July 15, 1968. Present doctor leaving area. 3 doctors from nearby towns on staff; group situation strong possibility. Beautiful 31 bed general hospital; 40 bed C&NC unit attached. Almost new clinic bldg. available; dental suite occupied. Area population near 5000 permanent residents; eight to ten thousand summer lake residents and tourists. Hospital located on shores of Onamia Lake; Famous Mille Lacs Lake only two miles distance. Many other desirable lakes for year 'round living close by. Town has 3 industries, Crosier Seminary, Good schools, churches. Two golf courses. Healthy place to live; fishing; hunting; summer and winter sports. Practice has excellent potential. Away from the maddening crowd, yet just a short distance to Minneapolis, St. Cloud and Brainerd. Make the move up to Onamia and Mille Lacs Lake where living is fun—where you'll have something to shout about. Contact M. Engstrom, Asst. Administrator, Community Mercy Hospital, Onamia, Minnesota. Phone (612) 532-3154.

WANTED: G.P. or Internist willing to do some G.P. Twin-towns totalling 12,000 western Minnesota Group now two G.P.'s and one FRCS surgeon. Modern clinic building with eight assistants, X-ray and minor laboratory, 125 bed accredited hospital. Rotating calls one night a week and every fifth week-end. Hunting, fishing, golfing available. Initial salary $1500.00 per month. Oportunity for partnership in one year. Apply to Louis T. O'Brien, M.D., Breckenridge, Minn.

FOR SALE: Practice—clinic—apartment bldg.—military-exempt town—will retire—14-room clinic-dental suite; 4 apartments. Apartments will retire costs. 2 good schools and churches—good farming area. New large swimming pool—18 hole golf course playable this summer—theatre—bowling alley. 17 miles from St. Olaf Hospital, Austin. Write—P. J. Schneider, M.D., Adams, Minn. 55909.

GENERAL SURGEON interested in some general practice to associate with a 2-man partnership in a rich agricultural community in southern Minnesota. Modern hospital and new clinic building. Hunting, 9-hole golf course, swimming pool. Salary open and full partnership as soon as desired. Write: Minnesota Medicine—405, 375 Jackson, St. Paul 55101.

WANTED: Physician wanted to join three-man group in fast-growing area just thirty minutes south of the Twin Cities. Will practice in a new clinic, new hospital and new nursing home. Salary and terms open. Contact M. H. Hunter, M.D., River's Edge Medical Clinic, Farmington, Minnesota. Telephone (612) 463-7181.

Minnesota Medicine at a Glance

Hydrocephalus—*Long et al.* Page 761

An extensive evaluation of the various ways hydrocephalus has been managed at the University of Minnesota Medical Center since 1938 is presented. Types of operative procedures, their complications and long-term results are compared. The ventriculo-atrial shunt is the operation of choice in the majority of cases of hydrocephalus.

Bilateral Spontaneous Massive Perirenal Hemorrhage—*Gambill et al.* Page 767

Perirenal bleeding in periarteritis is rare and bilateral perirenal hematomas rank as medical curiosities. The authors found four in the world literature and report the fifth case. The right-sided hemorrhage occurred five days after liver biopsy; the left two weeks later. The patient survived one month.

Coarctation of the Aorta in Veterans—*Beard and Sako* Page 775

A 19-year experience in dealing with coarctation of thoracic aorta is reviewed. Diagnostic features and treatment are considered. It is of considerable interest that a number of these patients had escaped detection and precise diagnosis, despite previous relatively complete physical examinations. A number had been considered malingerers.

Neointimae—*Shimamura et al.* Page 779

With the abundant developments of vascular surgery it is interesting to learn that a prosthetic aorta can develop for all practical purposes a serviceable intima within its lumen.

What's New?

Contraception without cerebration! Syntex announces its pill-a-day oral contraceptive, Noriday. This innovation consists of 21 white tablets containing 1 mg. of norethindrone and 0.05 mg. of mestranol plus seven orange tablets containing inert ingredients. This product is designed to avoid missed doses and miscalculations on the part of the woman taking contraceptive medication.

Lederle Laboratories announces a new anti-tuberculosis drug, Myambutol ethambutol. The drug is reported to be effective in cases of tuberculosis with drug-resistant organisms. Human studies with the drug have now been conducted for six years and one of the side effects associated with the drug has been the occasional reduction in visual acuity which is apparently reversible when the drug is discontinued. Myambutol appears to be highly specific against the tubercle bacillus, has a low incidence of side reaction and slow emergence of resistant strains. It has been used both alone and in combination with isoniazid or with streptomycin and isoniazid.

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Mrs. L. L. Bissinger	Seventh District	Brainerd
Mrs. John Rutledge	Eighth District	Detroit Lakes
Mrs. John Barker	Ninth District	Duluth

Chairmen of Committees

Archives—Mrs. John H. Peterson ..... Duluth

Bylaws—Mrs. Leo Fink ..... Minneapolis

Community Health, Pre-School Medical Survey of Vision and Hearing and Committee for the Aging—
Mrs. Chauncey Kelsey (Chairman) ..... St. Paul
Mrs. Sam Leonard (Co-Chairman) ... Minneapolis
Mrs. Robert D. Thielen (Co-Chairman) New Brighton

Disaster Preparedness and Safety and Rural Health—
Mrs. Roy J. Thurn ..... Duluth

Health Careers—Mrs. Ellery M. James ..... Mahtomedi

International Health Activities—Mrs. Howard Andersen ..... Rochester

Mental Health—Mrs. F. E. Ellison (Chairman) ..... Monticello
Mrs. Deane Petersen (Co-Chairman) ..... Edina

Finance—Mrs. Harold O. Peterson ..... St. Paul

In Memoriam—Mrs. Russell Lindgren ..... Edina

Program—Mrs. Cyril Tifft ..... St. Paul

AMA-ERF—Mrs. M. I. Shelander ..... St. Paul

Legislation—Mrs. James Flinn ..... Redwood Falls

Membership—Mrs. Josiah Fuller ..... Duluth

Editor—Gopher Doctor's Wife—
Mrs. Richard C. Horns ..... Edina

Press and Publicity—Mrs. Byron Cochrane .... St. Paul

Roster—Mrs. W. P. Gjerde ..... Lake City

Resolutions—Mrs. Karl Anderson ..... Excelsior

Social—Fall School of Instruction and Mid-Winter Board Meeting—
Mrs. Joseph G. Brennan, Edina
Mrs. Richard C. Tucker, Edina
Mrs. Thomas Wier, St. Paul
Mrs. George Schaffhausen, St. Paul
Mrs. Norval Westby, Madison
Mrs. John C. O'Brien, St. Paul
Mrs. Hamlin Mattson, Hopkins
Mrs. A. Don Walden, LeSueur

Advisory Committee—
Mrs. R. F. Erickson, Minneapolis
Mrs. Walter P. Gardner, St. Paul
Mrs. M. I. Hauge, Marcell
Mrs. L. P. Howell, Rochester
Mrs. Karl Johnson, Duluth
Mrs. F. W. Conley, Duluth


COUNTY MEDICAL SOCIETIES
OF THE
MINNESOTA STATE MEDICAL ASSOCIATION
Number of physicians in each county shown by figure in lower left corner.
RED RIVER VALLEY
HEADWATERS
RANGE
No. St. Louis Co.
So. St. Louis Co.
ST. LOUIS
CLAY-BECKER
UPPER MISSISSIPPI
PARK REGION DISTRICT
EAST CENTRAL MINNESOTA
WEST CENTRAL MINNESOTA
STEARNS-BENTON
KANDIYOHI-SWIFT-MEEKER
WRIGHT
WASHINGTON
RAMSEY
HENNEPIN
CAMP RELEASE DISTRICT
RENVILLE-REDWOOD
McLEOD
SCOTT
CARVER
SIBLEY
LYON-LINCOLN
NICOLLET
LE SUEUR
RICE
GOODHUE
WABASHA
BROWN
SOUTHWESTERN MINNESOTA
BLUE EARTH
WA-SECA
STEELE
ZUMBRO-WINONA
BLUE EARTH VALLEY
FREEBORN
MOWER
VALLEY

County Medical Society Roster

KEY TO SYMBOLS AS FOLLOWS

* Deceased
† Affiliated, Associated, Life, or Resident Members
Service
‡ Wife is Member of Woman's Auxiliary
¶ Honorary Member

BLUE EARTH COUNTY MEDICAL SOCIETY

Blue Earth County
Regular meetings, last Monday of the month
Annual meeting, December
Number of members 53

PRESIDENT
Heimark, J. J. ..... Mankato
SECRETARY
Fortier, R. G. ..... Mankato
‡ Anderson, Oscar D. ..... Mankato
‡ Arnesen, Paul M. ..... Mankato
‡ Barbarisi, Charles F. ..... Mankato
‡ Batdorf, B. Niles ..... Mankato
† Butzer, John A. ..... Mankato
Butzer, John F. ..... Mankato
‡ Chalgren, William S. ..... Mankato
‡ Conley, Robert H. ..... Mankato
Dobson, Mervin W. ..... Mankato
‡ Edwin, R. L. ..... No. Mankato
‡ Eisenbeis, C. F. ..... Mankato
Engstrom, Robert B. ..... Mankato
Eustermann, John J. ..... Mankato
‡ Flentje, Dale E. ..... Mankato
‡ Florine, Martin C. ..... Madison Lake
‡ Fortier, R. G. ..... Mankato
† Franchere, Frederick W. ..... Lake Crystal
Freeman, Donald H. ..... Mankato
‡ Geurs, Benjamin R. ..... Mankato
‡ Gislason, Paul H. ..... Mankato
‡ Grande, David W. ..... Mankato
‡ Hammar, Lawrence M. ..... Mankato
Hankerson, Robert G. ..... Mankato
‡ Heimark, John J. ..... Mankato
‡ Heller, Edgar E. ..... Mankato
‡ Hoeper, Philip G. ..... Mankato
Huffington, Herb L. ..... Waterville
† Huffington, Herbert L. ..... Lutsen
Jones, Orville H. ..... Mankato
‡ Kearney, R. Wynn ..... Mankato
† Kemp, Alphonse F. ..... Mankato
La Brec, H. C. ..... Mankato
Lester, John W. ..... Mapleton
‡ Lindblom, Alton E. ..... No. Mankato
† Luck, Hilda ..... Mankato
‡ Lund, J. Benjamin ..... Mankato
‡ Marso, John L. ..... Mankato
‡ Mathews, Wallace E. ..... Mankato
‡ Meredith, Donald C. ..... Mankato
‡ Mickelson, John C. ..... Los Angeles, Calif.
‡ Morgan, Hugh O. ..... Amboy
Olive, John T., Jr. ..... Mankato
Penn, George E. ..... Mankato
Roth, Frederick D. ..... Mankato
‡ Sanford, Raymond A. ..... Mankato
‡ Scheidel, A. M. ..... Mankato
‡ Schmitz, Anthony A. ..... Mankato
‡ Setzer, Hobert J., Jr. ..... Mankato
‡ Sjoding, J. Donald ..... Mankato
‡ Smith, Harry J. ..... Lake Crystal
‡ Snider, Howard R. ..... Mankato
Stillwell, Walter C. ..... Mankato
Strobel, Claire J. A. ..... Mankato
‡ Swenson, Donald B. ..... Mankato
Thiem, Chester E. ..... Mankato
† Troost, H. Bradley ..... Mankato
† Vezina, John C. ..... Mapleton
‡ Von Drasek, Joseph ..... Mankato
‡ Wahl, Donald H. ..... Mankato
† Wentworth, Albert J. ..... Mankato

BLUE EARTH VALLEY MEDICAL SOCIETY

Martin, Watonwan and Faribault Counties
Regular meetings, third Wednesday of each month
Annual meeting in November
Number of members 41

PRESIDENT
Halverson, Donald E. ..... Winnebago
SECRETARY
Boysen, Herbert ..... Madelia
‡ Anderson, John W. ..... Blue Earth
Armstrong, Ralph S. ..... Winnebago
‡ Bellomo, John ..... Fairmont
†‡ Bergman, Oscar B. ..... St. James
‡ Boysen, Herbert ..... Madelia
†‡ Bratrude, Earl J. ..... Hopkins
Cox, Russell L. ..... Estherville, Iowa
Cullen, Robert M. ..... Elmore
‡ Drexler, George W. ..... Blue Earth
‡ Feigal, William M. ..... Fairmont
‡ Gardner, Jack K. ..... Fairmont
†‡ Gardner, Victor H. ..... Fairmont
Halverson, Donald E. ..... Winnebago
‡ Halverson, William G. ..... Madelia
‡ Hanson, Lewis ..... Frost
‡ Hruza, William J. ..... Madelia
Kraemer, George N. ..... Fairmont
‡ Krause, Carl W. ..... Fairmont
‡ Lester, Malcolm J., Jr. ..... Truman
Lindahl, Merlyn J. ..... Sherburn
‡ Mattson, Albert D. ..... St. James
† Mills, John L. ..... Winnebago
‡ Moulton, Keith B. ..... St. James
‡ Nickerson, John R. ..... Fairmont
‡ Nickerson, Neil D. ..... Fairmont
†‡ Ourada, Anthony L. ..... St. Paul
‡ Parsons, R. A. ..... St. James
Parsons, Ralph L. ..... Trimont

Blue Earth Valley Medical Society (*Continued*)

Pitcher, Arlo L. ..... St. James
‡ Russ, Homer H. ..... Blue Earth
‡ Schulz, Robert W. ..... Fairmont
‡ Smith, Don V. ..... Blue Earth
‡ Snyder, Clifford D. ..... Kiester
‡ Thayer, Ellsworth A. ..... Fairmont
‡ Virnig, Mark P. ..... Wells
‡ Virnig, Richard P. ..... Wells
‡ Wandke, Otto E. ..... Fairmont
‡ Watkins, John A. ..... Wells
‡ Williamson, Harold A. ..... Fairmont
‡ Zemke, Erhart E. ..... Fairmont
Zemke, Robert L. ..... Fairmont

BROWN COUNTY MEDICAL SOCIETY

Brown County
Regular meetings, quarterly,
January, April, July, and October
Annual meeting in January
Number of members 25

PRESIDENT

Black, William A. ..... New Ulm

SECRETARY

Ringhofer, Lawrence ..... New Ulm
‡ Black, William A. ..... New Ulm
‡ Boyle, Francis J. ..... Springfield
‡ Burnett, Joseph W. ..... New Ulm
‡ Cairns, Robert J. ..... Redwood Falls
‡ Carthey, Frank J. ..... New Ulm
‡ Fesenmaier, Otto B. ..... Los Angeles, CA
† Fritsche, Albert ..... New Ulm
‡ Fritsche, Carl J. ..... New Ulm
‡ Fritsche, Theodore R. ..... New Ulm
Goblirsch, Andrew P. ..... Sleepy Eye
‡ Johnson, Rex R. ..... New Ulm
‡ Kaiser, Milton L. ..... New Ulm
‡ Keithahn, Elmer F. ..... Sleepy Eye
‡ Kitzberger, Peter J. ..... New Ulm
Muesing, William J. ..... New Ulm
† Nuessle, Walter G. ..... Springfield
‡ Penk, Engward L. ..... Springfield
Peterson, Roy A. ..... Vesta
‡ Rimas, Mathew J. ..... Comfrey
‡ Ringhofer, Lawrence ..... New Ulm
‡ Saffert, Cornelius A. ..... New Ulm
‡ Vogel, Howard A. L. ..... New Ulm
Wing, Elton G. ..... Sleepy Eye
‡ Wohlrabe, Donald E. ..... Springfield
‡ Wohlrabe, Edwin J. ..... Springfield

CAMP RELEASE DISTRICT MEDICAL SOCIETY

Chippewa, Lac qui Parle and Yellow Medicine Counties
Regular meetings, third Thursday of each month
except July and August
Annual meeting, November
Number of members 25

PRESIDENT

Maus, Philip W. ..... Dawson

SECRETARY

Lundell, Carl L. ..... Granite Falls
‡ Allen, John H. ..... Montevideo
‡ Anderson, Chester A. ..... Madison
‡ Birkey, Thomas G. ..... Montevideo
‡ Boody, George J. ..... Cambridge
‡ Burns, Floyd M. ..... Milan
† Burns, M. A. ..... Milan
‡ Camp, Ray J. ..... Madison
‡ Gustafson, Robert W. ..... Granite Falls
‡ Hagberg, Norman L. ..... Montevideo
†‡ Hauge, Malvin I. ..... Marcell
*† Holmberg, LeRoy J. ..... Canby
‡ Johnson, Vilhelm M. ..... Dawson
† Jordan, Kathleen B. Smith ..... Granite Falls
Karrow, John W. ..... Granite Falls
†‡ Kaufman, William C. ..... Appleton
‡ Kremer, Jerome L. ..... Montevideo
‡ Lima, Ludvig R. ..... Montevideo
‡ Lundell, Carl L. ..... Granite Falls
‡ Maus, Philip W. ..... Dawson
‡ Niazi, Suad A. ..... Granite Falls
‡ Odland, Olin M. ..... Granite Falls
‡ Owens, William A. ..... Montevideo
Radke, Robert L. ..... Montevideo
‡ Roust, Henry A. ..... Montevideo
‡ Schmidt, Paul G. ..... Granite Falls
‡ Westby, Norval M. ..... Madison

CLAY-BECKER COUNTY MEDICAL SOCIETY

Clay and Becker Counties
Regular meetings, two per year
Annual meeting, December
Number of members 27

PRESIDENT

Brenk, Paul E. ..... Detroit Lakes

SECRETARY

Saxman, Gertrude O. ..... Ulen
Bigler, Earl E. ..... Perham
Bigler, Ivan E. ..... Perham
Bologna, Camillo V. ..... Moorhead
† Bottolfson, B. T. ..... Moorhead
‡ Brenk, Paul E. ..... Detroit Lakes
‡ Carlon, Donald L. ..... Moorhead
‡ Carlson, Vernon J. ..... Moorhead
Covey, Kenneth W. ..... Moorhead
‡ Dodds, William C. ..... Detroit Lakes
‡ Duncan, James W. ..... Moorhead
‡ Geib, Marvin J. ..... Fargo, ND
‡ Holten, John ..... Moorhead
Johnson, Olga H. ..... Moorhead
‡ Knapp, James F. ..... Detroit Lakes
Koons, William R. ..... Mahnomen
‡ Lorentzen, Ernest S. ..... Detroit Lakes
‡ Midthune, Andreen S. ..... Lake Park
‡ Moberg, Clarence W. ..... Detroit Lakes
Odland, Mark E. ..... Detroit Lakes
‡ Rice, Hagbart G. ..... Moorhead
‡ Rutledge, John B. ..... Detroit Lakes
†‡ Rutledge, Lloyd H. ..... Detroit Lakes
Saxman Gertrude O. ..... Ulen
‡ Simison, Carl ..... Barnesville
‡ Thysell, Vernon D. ..... Moorhead
‡ Watson, Robert N. ..... Detroit Lakes
‡ Watson, Virgil A. ..... Detroit Lakes

EAST CENTRAL MINNESOTA MEDICAL SOCIETY

Anoka, Chisago, Isanti, Kanabec, Mille Lacs,
Pine and Sherburne Counties
Regular meetings first Tuesday of even
months of the year
Annual meeting, first Tuesday in December
Number of members 35

PRESIDENT

Seecamp, Carsten H. ..... Cambridge

SECRETARY

Sommer, Robert K. ..... Elk River
Ahlstrom, Robert C. ..... Braham
Aruguete, Alayne ..... Sandstone
Aruguete, Jose ..... Sandstone
Berge, Harry L. ..... Mora
Berglund, Alvin E. ..... Cambridge
Bunker, Bevan W. ..... Anoka
‡ Burseth, Edgar C. ..... Mora
Courteau, Robert D. ..... Onamia
‡ Deason, Keith B. ..... Chisago City
Doebler, Myron I. ..... Mora
Gailitis, Veronika M. ..... St. Paul
Grinvalds, Anna O. ..... Cambridge
Halpin, Joseph E. ..... Rush City
Hilgedick, Wm. R. ..... St. Paul
‡ Hovde, Gordon W. ..... Chisago City
Huber, Robert W. ..... St. Croix Falls, WI
Hubin, Edwin G. ..... Sandstone
Johnson, Aldridge F. ..... St. Paul
*‡ Kapsner, Alfred ..... Princeton
† Kelsey, Carleton G. ..... St. Paul
Larson, Gerald E. ..... Cambridge
‡ Lindquist, Dale C. ..... Lindstrom
‡ McManus, William F. ..... Princeton
Mach, Ralph F. ..... Pine City
Magnuson, Raymond C. ..... Cambridge
† Metcalf, Norman B. ..... Princeton
Nelson, Luther A. ..... Rush City
‡ Nordman, Willard F. ..... Mora
Nygren, William T. ..... Braham
Peterson, Alvin C. ..... Mora
Pivac (Popovich) Dragojla ..... Milwaukee, WI
Reiners, Gary ..... Cambridge
‡ Roehlke, Arthur B. ..... Elk River
Sander, John L. ..... Cambridge
† Schut, John W. ..... Anoka
Seecamp, Carsten H. ..... Cambridge
Sommer, Robert K. ..... Elk River
† Spurzem, Raymond J. ..... Anoka
†‡ Stratte, Alf K. ..... Pine City
‡ Swenson, Roy G. ..... North Branch
‡ Tesch, Gordon H. ..... Elk River
Textor, Jerome ..... Anoka
‡ Travis, Richard C. ..... Elk River
*† Waller, Joseph D. ..... Pine City

FREEBORN COUNTY MEDICAL SOCIETY

Freeborn County
Regular meetings, third Thursday of even months
Annual meeting, December
Number of members 31

PRESIDENT

Bartness, John E. ..... Albert Lea

SECRETARY

Ellertson, Leonard M. ..... Albert Lea
‡ Barr, Lowell C. ..... Albert Lea
‡ Barr, Lowell, W. ..... Albert Lea
‡ Bartness, John E. ..... Albert Lea
‡ Blumer, Arlo R. ..... Albert Lea
† Burns, Catherine ..... Excelsior
† Calhoun, Frank W. ..... Albert Lea
‡ Campbell, John C. ..... Albert Lea
‡ Cole, George A. ..... Albert Lea
‡ Demo, Robert A. ..... Albert Lea

Freeborn County Medical Society (*Continued*)

‡ Donovan, Daniel L. ..... New Brighton
‡ Egge, Sanford G. ..... Albert Lea
‡ Ellertson, Leonard M. ..... Albert Lea
Erdal, Ove A. ..... Columbia, Mo.
†‡ Gamble, Elbert J. ..... Roseville
‡ Gill, Theodore M. ..... Albert Lea
‡ Hansen, Theodore M. ..... Albert Lea
‡ Keil, Marcus A. ..... Albert Lea
† Leopard, Brand A. ..... Brownsville, TX
‡ Menefee, Edward C. ..... Albert Lea
‡ Myers, Theodore P. ..... Albert Lea
‡ Neel, Harry B. ..... Albert Lea
‡ Nelson, Clayton E. J. ..... Albert Lea
‡ Nesheim, Martin O. ..... Emmons
‡ Palmer, Clinton F. ..... Albert Lea
‡ Schmidt, Ruben F. ..... Alden
‡ Shepard, Richard ..... Albert Lea
‡ Sherman, Alfred G. ..... Albert Lea
‡ Steiner, Leon E. ..... Albert Lea
‡ Stoker, Lynn C. ..... Albert Lea
‡ Whitson, Sidney A. ..... Albert Lea
‡ Wilcox, G. Charles ..... Albert Lea

GOODHUE COUNTY MEDICAL SOCIETY

Goodhue County
Regular meeting, April
Annual meeting, December
Number of members 22

PRESIDENT
Brusegard, James F. ..... Red Wing

SECRETARY
Rayner, Ralph R. ..... Red Wing

‡ Akins, Willard M. ..... Red Wing
‡ Billings, Harry H. ..... Red Wing
‡ Brusegard, James F. ..... Red Wing
‡ Cant, Wilbur F. ..... Red Wing
‡ Delahunty, John R. ..... Red Wing
Douglass, Jesse E. ..... Cannon Falls
Falls, John L. ..... Red Wing
‡ Halvorson, James W. ..... Zumbrota
‡ Hartnagel, Grant F. ..... Red Wing
‡ Hawley, George M. B. ..... Red Wing
‡ Jackish, George E. ..... Red Wing
‡ Juers, Edward H. ..... Red Wing
‡ Larson, Oliver E. H. ..... Zumbrota
†‡ Liffrig, William W. ..... Red Wing
‡ Molenaar, Robert E. ..... Cannon Falls
Nicolay, William R. ..... Red Wing
‡ Rayner, Ralph R. ..... Red Wing
Schroeder, Glenn E. ..... Red Wing
‡ Sherman, Royal V. ..... Red Wing
† Steffens, Leon ..... Red Wing
‡ Walter, William E. ..... Wanamingo
‡ Wasmund, Clarence W. ..... Red Wing
‡ Williams, Marland R. ..... Cannon Falls

HEADWATERS MEDICAL SOCIETY

Beltrami, Clearwater and Lake of the Woods Counties
Regular meetings, to be determined
Annual meeting, 2nd Saturday in September
Number of members 22

PRESIDENT
Palmer, Harry A. ..... Blackduck

SECRETARY
Groschupf, Richard P. ..... Bemidji
Brink, Adlai A. ..... Baudette
Deweese, Wilford J. ..... Bemidji
Franklin, Gordon W. ..... Northome
Gregoire, Earl ..... Bemidji
Griffin, John W. ..... Bemidji
Groschupf, Richard P. ..... Bemidji
† Groschupf, Theophilus P. ..... Bemidji
Hartjen, Jason K. ..... Bemidji
Hildebrand, John E. ..... Bemidji
Hoganson, Donald E. ..... Bemidji
Janecky, Allen G. ..... Baudette
† Johnson, Einer W. ..... Bemidji
LaLonde, John B. ..... Bemidji
Larson, Leroy J. ..... Bagley
Lundsten, Leslie C. ..... Bemidji
Pearson, Harris L. ..... Bagley
Palmer, Harry A. ..... Blackduck
Reeber, Erick ..... Bagley
Reid, Howard ..... Bemidji
Roholt, Hartvig B. ..... Bemidji
Thompson, James R. ..... Bemidji
Whittemore, Dexter D. ..... Bemidji

HENNEPIN COUNTY MEDICAL SOCIETY

Hennepin County
Regular meetings, first Monday of the Months of October, January, March and May, except when otherwise designated
Annual meeting, first Monday in October
Number of members 1373

PRESIDENT
Correa, Dale H. ..... Minneapolis
SECRETARY
Mankey, James C. ..... Minneapolis
EXECUTIVE SECRETARY
Cook, Thomas P., Mr. ..... Minneapolis
‡ Abramson, Burton I. ..... Minneapolis
Abrahamson, Michael B. ..... Oakland, CA
Abramson, Milton ..... Minneapolis
‡ Abullarade, Jose A. ..... Minneapolis
‡ Abuzzahab, Faruk S. ..... Minneapolis
Adams, Brandon L. W. ..... Minneapolis
Adams, Richard I. ..... Minneapolis
Adcock, Leon ..... Minneapolis
‡ Adkins, C. Douglas ..... Minneapolis
Adkins, James T. ..... Coon Rapids
‡ Agustsson, Hreidar ..... Minneapolis
‡ Ahern, Eugene E. ..... Minneapolis
Alari, Heino ..... Excelsior
‡ Alexander, Harlan A. ..... Minneapolis
‡ Aling, Charles A. ..... Minneapolis
‡ Allen, James R. ..... Minneapolis
Alter, Milton ..... Minneapolis
† Altnow, Hugo O. ..... Coral Gables, FL
‡ Amatuzio, Donald S. ..... Minneapolis
‡ Amren, Don P. ..... Minneapolis
‡ Andregg, Alfred F. ..... St. Paul
‡ Andersen, James G. ..... Minneapolis
‡ Anderson, Arnold S. ..... Minneapolis
Anderson, Ben H. ..... Minneapolis
‡ Anderson, David M. ..... Minneapolis
*† Anderson, Edward D. ..... Vaud, Switzerland
‡ Anderson, Ernest R. ..... Minneapolis
‡ Anderson, Frank J. ..... Minneapolis
Anderson, John A. ..... Minneapolis
†‡ Anderson, Karl W. ..... Excelsior
Anderson, Richard W. ..... Minneapolis
Anderson, Roger E. ..... Minneapolis
‡ Anderson, Roger L. ..... Minneapolis
Anderson, Thomas P. ..... Minneapolis
Anderson, U. Schuyler ..... Edina
Anderson, Wallace E. ..... Minneapolis
Anderson, Wallace R. ..... Minneapolis
‡ Anderson, William H. ..... Minneapolis
Anderson, William T. ..... Minneapolis
Anderson, W. Robert ..... Minneapolis
†‡ Andreassen, Einar C. ..... Minneapolis
‡ Andreassen, Rolf L. ..... Minneapolis
‡ Andresen, Karl d'A ..... Minneapolis
‡ Ankner, Frank J. ..... Minneapolis
‡ Anonsen, Richard E. ..... Minneapolis
Anselment, Lois A. ..... Excelsior
† Antolak, Stanley J., Jr. ..... Minneapolis
† Arends, Archabald L. ..... Minneapolis
‡ Arey, Stuart Lane ..... Minneapolis
‡ Arhelger, Stuart W. ..... Minneapolis
‡ Arlander, Clarence E. ..... Minneapolis
‡ Arling, Leonard S. ..... Minneapolis
‡ Arms, James J. ..... Minneapolis
Armstrong, Byron H. ..... Minneapolis
† Arnold, Ann W. ..... Minneapolis
Arnold, Thomas B. ..... Minneapolis
‡ Aughenbaugh, John W. ..... Minneapolis
† Aust, John C. ..... Minneapolis
Avant, Robert F. ..... Minneapolis
Azad, A. M. ..... Minneapolis
‡ Baggenstoss, Osmond J. ..... Minneapolis
‡ Bagley, Russell W. ..... Minneapolis
‡ Baken, Melvin P. ..... Minneapolis
Baken, Melvin P., Jr. ..... Minneapolis
Baker, Abe B. ..... Minneapolis
‡ Baker, C. Camak ..... Minneapolis
† Baker, Daniel R. ..... Minneapolis
‡ Baker, Milton E. ..... Minneapolis
Bakke, Arnold C. ..... Minneapolis
*‡ Baleisis, Peter ..... Minneapolis
‡ Balkin, Samuel G. ..... Minneapolis
Balkins, John W. ..... Minneapolis
‡ Balogh, Charles J. ..... Minneapolis
† Bank, Harry E. ..... Minneapolis
Banovetz, John D. ..... Minneapolis
‡ Barnett, Robert M. ..... Minneapolis
‡ Barno, Alex ..... Minneapolis
‡ Barr, Maxwell M. ..... Minneapolis
Barr, Robert N. ..... Minneapolis
Barrett, Patrick J. ..... Minneapolis
‡ Barron, Jesse J. ..... Minneapolis
†‡ Barron, Moses ..... Beverly Hills, CA
‡ Barry, George J. ..... Minneapolis
‡ Beach, Northrop ..... Minneapolis
Beard, Archibald H., Jr. ..... Minneapolis
‡ Becklund, Roger W. ..... Minneapolis
Beeman, John A. ..... Minneapolis
‡ Beirstein, Samuel ..... Minneapolis
‡ Beiswanger, Richard H. ..... Minneapolis
‡ Bell, Donald C. ..... Minneapolis
Bellville, Titus P. ..... Minneapolis
‡ Belzer, Meyer S. ..... Minneapolis
Bendel, William L., Jr. ..... Coon Rapids
Benesh, Louis A. ..... Minneapolis
‡ Benjamin, Edwin G. ..... Minneapolis
‡ Benjamin, Harold G. ..... Minneapolis
Benjamin Richard D. ..... Minneapolis
‡ Benjamin, Robert B. ..... Minneapolis
Bentz, Herman D. ..... Anoka
‡ Berestka, Stephen J. ..... Minneapolis
Berg, Clinton C. ..... Excelsior
Berger, Alex G. ..... Minneapolis
‡ Bergh, George S. ..... Minneapolis
Bergh, Solveig M. ..... Minneapolis
‡ Berglund, Eldon B. ..... Minneapolis
‡ Bergquist, James R. ..... Minneapolis
Bergstrom, Ralph W., Jr. ..... Maple Plain
‡ Berkwitz, Nathaniel J. ..... Minneapolis
Berman, David A. ..... Minneapolis
Berman, Reuben ..... Minneapolis
Bernstein, Irving C. ..... Minneapolis
‡ Berris, Harold ..... Minneapolis
‡ Berry, Ronald N. ..... Minneapolis

Hennepin County Medical Society *(Continued)*

Berzins, Rainis ..... Minneapolis
†‡ Bessesen, Alfred N. ..... Minneapolis
‡ Bevis, William D. ..... Minneapolis
Bieter, Raymond N. ..... Minneapolis
Bilka, Paul J. ..... Minneapolis
Billman, Herbert R. ..... Minneapolis
‡ Binder, Manuel R. ..... Minneapolis
Bittick, Wilbur H. ..... Minneapolis
‡ Blackard, Clyde E. ..... Minneapolis
‡ Blake, Allan J. ..... Hopkins
‡ Blake, James A. ..... Hopkins
‡ Blake, Paul S. ..... Minneapolis
Blaw, Michael E. ..... Minneapolis
Bloch, Henry S. ..... Minneapolis
‡ Bloedel, Traugott J. ..... Osseo
‡ Blomberg, Robert D. ..... Minneapolis
‡ Bloom, David ..... Minneapolis
‡ Bloom, Norman B. ..... Minneapolis
‡ Blumenthal, Malcolm N. ..... Minneapolis
Boardman, William J. ..... Minneapolis
‡ Bofenkamp, Benjamin ..... Minneapolis
‡ Bohn, Donald G. ..... Minneapolis
‡ Boies, Lawrence R., Sr. ..... Hopkins
Boies, Lawrence R., Jr. ..... Wayzata
‡ Bolt, Donald A. ..... Miinneapolis
‡ Borman, Chauncey N. ..... Minneapolis
‡ Borowicz, Leonard A. ..... Minneapolis
Bouthilet, Florence J. ..... Minneapolis
‡ Bowers, Gordon G. ..... Minnetonka
‡ Bowlin, Paul F. ..... Minneapolis
† Boynton, Ruth E. ..... Miami, FL
Bradley, Jeanne B. ..... Minneapolis
Bradley, John G. ..... Minneapolis
Bradley, William E. ..... Minneapolis
‡ Brandt, Henry E. ..... Minneapolis
Bransford, Paul W. ..... Minneapolis
‡ Brauer, William W. ..... Minneapolis
‡ Braun, Rene ..... Minneapolis
Breitenbucher, Robert B. ..... Minneapolis
‡ Brekke, Harvey J. ..... Minneapolis
‡ Brennan, Joseph G. ..... Minneapolis
Brill, Alice K. ..... Minneapolis
‡ Briones, Bienvenido R. ..... Hopkins
† Brooks, Charles N. ..... Wayzata
‡ Brown, John H. ..... Minneapolis
* Brown, William D. ..... Minneapolis
Brown, William D., Jr. ..... Minneapolis
‡ Buchstein, Harold F. ..... Minneapolis
‡ Buckley, Joseph J. ..... Minneapolis
‡ Bugby, Robert D. ..... Minneapolis
‡ Bugenstein, Robert H. ..... Minneapolis
‡ Buie, Louis A., Jr. ..... Minneapolis
‡ Buirge, Raymond E. ..... Minneapolis
‡ Bundt, Robert E. ..... Minneapolis
Buran, David J. ..... Minneapolis
Burkholder, Dayton D. ..... Anoka
‡ Burnham, Wesley H. ..... Minneapolis
Burton, Thomas P. ..... Minneapolis
‡ Cable, Morris L. ..... Minneapolis
‡ Cabot, Clyde M. ..... Minneapolis
Calin, S. Hartley ..... Minneapolis
† Cameron, Isabell L. ..... Minneapolis
‡ Campbell, Denis V. ..... Minneapolis
‡ Campbell, Orwood J. ..... Minneapolis
‡ Caplan, Leslie ..... Minneapolis
‡ Card, William H. ..... Minneapolis
Cardle, James G. ..... Minneapolis
‡ Cardle, John B. ..... Minneapolis
Carey, James B., Jr. ..... Minneapolis
‡ Carlander, Lester W. ..... Minneapolis
‡ Carlson, Charles V. ..... Mound
† Carlson, Erik E. ..... Hopkins
‡ Carlson, Lawrence ..... Minneapolis
Carlson, Robert G. ..... Anoka
‡ Caron, Robert P. ..... Minneapolis
‡ Carr, William J. ..... Minneapolis
Carrier, Thomas C. ..... Minneapolis
‡ Caspers, Carl G. ..... Minneapolis
‡ Cauble, Charles F. ..... Minneapolis
†‡ Cavanor, Frank T. ..... Minneapolis
Cavert, H. Mead ..... Minneapolis
‡ Ceder, Elmer T. ..... Minneapolis
‡ Cella, Joseph A. ..... Minneapolis
‡ Chadbourn, Wayne A. ..... Minneapolis
Challman, S. Alan ..... Minneapolis
#‡Chandler, William M. ..... Great Lakes, IL
‡ Chedister, Charles R. ..... Minneapolis
‡ Chesler, Merrill D. ..... Minneapolis
Child, Sherman B. ..... Minneapolis
‡ Chisholm, Tague C. ..... Minneapolis
Chou, Shelley N. .. .. Minneapolis
‡ Christensen, Llewellyn E. ..... Minneapolis
Christenson, Leland R. ..... Maple Plain
Christgau, Roger A. ..... Minneapolis
Clark, Malcolm D. ..... Minneapolis
‡ Clark, Robert S. ..... Minneapolis
‡ Clay, Lyman B. ..... Minneapolis
‡ Cochrane, Ray F. ..... Minneapolis
Coe, John I. ..... Minneapolis
‡ Cohen, Bernard A. ..... Minneapolis
Cohen, Ephraim B. ..... Minneapolis
‡ Cohen, Henry W. ..... Wayzata
‡ Cohen, Sumner S. ..... Minneapolis
‡ Cole, James S. ..... Minneapolis
Coleman, Thomas P. ..... Minneapolis
‡ Conlin, F. Dixon ..... Minneapolis
Conlon, Daniel C. ..... Minneapolis
† Connor, David G. ..... Minneapolis
‡ Cooper, John P. ..... Minneapolis
‡ Cooper, Robert R. ..... Minneapolis
† Corniea, Albert D. ..... Minneapolis
‡ Correa, Dale H. ..... Minneapolis
‡ Cortez, Daniel P. ..... Minneapolis
‡ Coulter, Harold E. ..... Minneapolis
Cowan, Donald W. ..... Minneapolis
Craig, M. Elizabeth ..... Minneapolis
‡† Cranmer, Richard R. ..... Minneapolis
Cranston, Robert W. ..... Minneapolis
‡ Creevy, Charles D. ..... Minneapolis
‡ Crowley, Leonard V. ..... Minneapolis
† Crutchfield, Susan E. ..... Fairchild AFB, WA
‡ Cullado, Andrionico F. ..... Minneapolis
‡ Culligan, Leo C. ..... Minneapolis
‡ Cundy, Donald T. ..... Minneapolis
Curran, John P. ..... Anoka
Cushing, Richard T. ..... Minneapolis
† Cutts, George ..... Minneapolis
‡ Daggett, Donald R. ..... Minneapolis
†‡ Dahl, Elmer O. ..... Minneapolis
Dahl, James C. ..... Minneapolis
† Dahl, John A. ..... Minneapolis
D'Angio, Giulio J. ..... Minneapolis
† Daniel, Donald H. ..... Minneapolis
‡ Danyluk, Michael ..... Minneapolis
Dargay, Cyril P. ..... Minneapolis
‡ David, Reuben ..... Hopkins

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Hennepin County Medical Society *(Continued)*

† Davis, Jay C. ..... Pompano Beach, FL
#‡Davis, Michael W. ..... A.P.O. New York, NY
Davis, Thomas S. ..... Minneapolis
Dawson, Walter J., Jr. ..... Minneapolis
Dedeker, Kenneth L. ..... Minneapolis
Delzell, Allen W. ..... Minneapolis
* Devereaux, Thomas J. ..... Wayzata
Diamond, Robert A. ..... Minneapolis
‡ Diefenbach, Eugene J. ..... Minneapolis
† Diehl, Harold S. ..... New York, NY
‡ Dierker, Heinrich A. ..... Minneapolis
† Diessner, Henry D. ..... Minneapolis
‡ Doan, Robert E. ..... Wayzata
‡ Docherty, John A. ..... Minneapolis
‡ Donatelle, Edward P. ..... Minneapolis
† Dorge, Richard ..... Minneapolis
Dornbach, Robert A. ..... Minneapolis
‡ Dorsey, George C., Jr. ..... Minneapolis
‡ Dorsey, William E. ..... Minneapolis
Doscherholmen, Alfred ..... Minneapolis
‡ Dougan, Jerome W. ..... Minneapolis
† Doxey, Gilbert L. ..... Minneapolis
‡ Dredge, Thomas E., Sr. ..... Minneapolis
‡ Dredge, Thomas E., Jr. ..... Minneapolis
‡ Drill, Frederick E. ..... Minneapolis
‡ Drill, Herman E. ..... Hopkins
‡ Duff, Edwin R. ..... Minneapolis
Duffy, John C. ..... Minneapolis
Dummer, Donald J. ..... New Brighton
Duncan, Donald A. ..... Minneapolis
‡ Dunlap, Earl H. ..... Minneapolis
‡ Dupont, Joseph A. ..... Excelsior
Duryea, Marbry ..... Minneapolis
‡ Duryea, Willis M. ..... Minneapolis
Duryea, Willis M., Jr. ..... Minneapolis
‡ Dvorak, Benjamin A. ..... Minneapolis
‡ Dwan, Paul F. ..... Minneapolis
†‡ Dworsky, Samuel D. ..... Minneapolis

Ebert, Richard ..... Minneapolis
Earl, Stephan H. ..... Minneapolis
Eckerly, Jean R. ..... Minneapolis
‡ Eder, Walter P. ..... Minneapolis
Edmondson, Hugh A., Jr. ..... Minneapolis
‡ Efteland, Myles E. ..... Minneapolis
† Ehrenberg, Claude J. ..... Boca Raton, FL
‡ Ehrlich, S. Paul ..... Minneapolis
Eich, Matthew A. ..... Minneapolis
Eichenlaub, John E. ..... Minneapolis
‡ Eichhorn, Edmund P., Jr. ..... Minneapolis
† Eisenstadt, David H. ..... Minneapolis
‡ Eisenstadt, William S. ..... Minneapolis
Eitel, George D. ..... Minneapolis
† Ekdale, Robert A. ..... Palo Alto, CA
‡ Ellingson, Richard B. ..... Minneapolis
‡ Ellison, Evan S. ..... Minneapolis
Elwood, Paul M., Jr. ..... Minneapolis
Emond, Joseph S. ..... Farmington
Emond, Joseph S., Jr. ..... Minneapolis
‡ Engel, Joseph P. ..... Minneapolis
*† Engelhart, Peter C. ..... Minneapolis
‡ Englund, Elvin F. ..... Minneapolis
†‡ Engstrand, Oscar J. ..... Minneapolis
‡ Engstrom, E. Duane ..... Minneapolis
‡ Engwall, Richard L. ..... Minnetonka
‡ Erickson, Clifford O. ..... Minneapolis
‡ Erickson, Laurence F. ..... Minneapolis
‡ Erickson, Myron E. ..... Minneapolis
Erickson, Reuben F. ..... Minneapolis
† Ersek, Robert A. ..... Minneapolis
‡ Esensten, Sidney ..... Minneapolis
Ettinger, Milton G. ..... Minneapolis
Etzwiler, Donnell D. ..... Minneapolis
‡ Evans, Edward T. ..... Minneapolis
Everhart, Francis J. ..... Minneapolis

† Fahr, George P. ..... Minneapolis
† Fallon, Virgil T. ..... Minneapolis
‡ Farber, Lawrence A. ..... Minneapolis
Farley, Harrison H. ..... Minneapolis
Farrell, T. Edwin ..... Minneapolis
† Feeney, John M. ..... Excelsior
‡ Feigal, David W. ..... Wayzata
Feinberg, Philip ..... Minneapolis
Feinberg, Samuel B. ..... Minneapolis
‡ Feinstein, Julius Y. ..... Minneapolis
†‡ Fenger, Ejvind P. K. ..... Chanhassen
‡ Fernandez, Rafael F., Jr. ..... Minneapolis
Fetzek, Albert D. ..... Minneapolis
‡ Field, Charles W. ..... Minneapolis
Fifer, Ellen Z. ..... St. Paul
Fifer, William R. ..... Minneapolis
Filiatrault, L. J. ..... Coon Rapids
‡ Filipovich, Orest N. ..... Minneapolis
‡ Fingerman, David L. ..... Minneapolis
‡ Fink, Leo W. ..... Minneapolis
‡ Fink, Robert J. ..... Minneapolis
† Fink, Walter H. ..... Minneapolis
Finlayson, Richard E. ..... Minneapolis
Fisher, Don H. ..... Minneapolis
Fisher, Isadore ..... Minneapolis
*† Fjeldstad, C. Alford ..... Minneapolis
‡ Fleming, Dean S. ..... Minneapolis
‡ Fliehr, Richard R. ..... Minneapolis
Flora, George C. ..... Minneapolis
‡ Florence, David W. ..... Minneapolis
Flory, William D. ..... Minneapolis
† Fluegel, John O. ..... Minneapolis
Foker, Leslie W. ..... Minneapolis
Foley, Robert R. ..... Minneapolis
‡ Foley, William A. ..... Minneapolis
‡ Folsom, Louis B. ..... Minneapolis
‡ Forbes, Edward F. ..... Minneapolis
‡ Ford, W. Harold ..... Hopkins
‡ Foster, Orley W. ..... Minneapolis
‡ Fox, James Rogers ..... Minneapolis
‡ Frane, Donald B. ..... Minneapolis
‡ Frane, Gerald T. ..... Minneapolis
Fredericks, George M. ..... Minneapolis
‡ Freeman, Craig W. ..... Minneapolis
Freeman, Donald W. ..... St. Louis Park
‡ French, Lyle A. ..... Minneapolis
‡ Frey, Richard J. ..... Minneapolis
Friberg, Joseph B. ..... Minneapolis
‡ Fried, Louis A. ..... Minneapolis
†‡ Friedell, Aaron ..... Minneapolis
Friedell, George ..... Minneapolis
‡ Friedman, Harry S. ..... Minneapolis
‡ Friend, Charles A. ..... Minneapolis
‡ Frost, John B. ..... Minneapolis
* Frost, Russell H. ..... Minneapolis
Fruchtman, Stanley A. ..... Minneapolis
‡ Frykman, Howard M. ..... Minneapolis
‡ Frys, Russell N. ..... Minneapolis
‡ Fuglestad, Edson V. ..... Minneapolis
‡ Fulks, Raymond W. ..... Minneapolis
† Fuller, Alice H. ..... Minneapolis
‡ Funk, Victor K. ..... Hopkins

Hennepin County Medical Society *(Continued)*

Furman, L. Christine ..... Minneapolis
Fusaro, Ramon M. ..... Minneapolis

Gaard, Richard C. ..... Robbinsdale
Galbraith, Richard F. ..... Minneapolis
Galejs, Aina ..... Minneapolis
‡ Gallett, Lester E. ..... Minneapolis
† Galligan, Margaret Mary D. ..... Minneapolis
Galway, Charles F. ..... Minneapolis
Gamble, William G. ..... Minneapolis
*†‡Gammell, John H. ..... Minneapolis
Gannon, Paul G. ..... Minneapolis
‡ Garamella, Joseph J. ..... Minneapolis
Garetz, Floyd K. ..... Minneapolis
‡ Garske, George L. ..... Minneapolis
Garten, Joseph L. ..... Minneapolis
‡ Garvey, James T. ..... Minneapolis
Gault, Neal L., Jr. ..... San Francisco, CA
‡ Gaviser, David ..... Minneapolis
‡ Geller, Joseph ..... Minneapolis
‡ George, Vane P., Jr. ..... Le Sueur
Gerster, Paul W. ..... Anoka
‡ Gibbs, Robert W. ..... Minneapolis
‡ Giebenhain, John N. ..... Minneapolis
‡ Giere, Joseph C. ..... Minneapolis
Giere, Richard W. ..... Minneapolis
Gilbert, Maurice G. ..... Minneapolis
Gilbertsen, A. Sigrid ..... Minneapolis
Gilbertsen, Victor A. ..... Minneapolis
Gilles, Paul J. ..... Great Lakes, IL
Gingold, Benjamin A. ..... Minneapolis
Glaeser, John H. ..... Minneapolis
‡ Godfrey, H. Wilson ..... Minneapolis
Gokcen, Barbara W. ..... Minneapolis
Gokcen, Muharrem ..... Minneapolis
Gold, David ..... Minneapolis
‡ Goldberg, Isadore M. ..... Minneapolis
Goldberg, Marvin E. ..... Minneapolis
‡ Goldberg, Stanley M. ..... Minneapolis
Goldfarb, Benjie L. ..... Minneapolis
Goldfarb, Mace G. ..... Minneapolis
†‡ Goldman, Theodore I. ..... Minneapolis
‡ Goldner, Meyer Z. ..... Minneapolis
Goldstein, Alan L. ..... Hopkins
‡ Good, Gary ..... Minneapolis
Goodchild, William R. ..... Minneapolis
Gordon, John R. ..... Minneapolis
Gordon, Sewell S. ..... Minneapolis
Gozum, Ekrem ..... Minneapolis
‡ Granquist, Richard D. ..... Minneapolis
Grant, Suzanne ..... Minneapolis
† Gratzek, Frank R. ..... Anoka
† Gray, Royal C. ..... Minneapolis
Green, Clayton R. ..... Excelsior
Green, Robert A. ..... Minneapolis
‡ Greenberg, Albert J. ..... Minneapolis
Greene, Leonard H. ..... Minneapolis
‡ Greenfield, Irving ..... Minneapolis
Greenwald, Stephen M. ..... Minneapolis
¶ Greisheimer, Esther M. ..... Philadelphia, PA
Grimes, Marian ..... Minneapolis
‡ Grimmell, Francis J. ..... Minneapolis
‡ Grismer, Jerome T. ..... Minneapolis
† Gronvall, Paul R. ..... Hopkins
*‡ Grotting, John K. ..... Minneapolis
‡ Gruys, Robert I. ..... Minneapolis
Guerrero, Rafael A. ..... Minneapolis
Gullickson, Glenn, Jr. ..... Minneapolis
‡ Gunlaugson, Frederick G. ..... Minneapolis
‡ Gustafson, Paul O. ..... Minneapolis
‡ Gustason, Harold T. ..... Minneapolis
Gustilo, Ramon B. ..... Minneapolis
Haas, John W. ..... Minneapolis
Haberer, Helen R. ..... Minneapolis
‡ Haberle, Charles A. ..... Minneapolis
‡ Hagen, Kristofer ..... Minneapolis
‡ Hagen, Wayne S. ..... Minneapolis
Haglin, John J. ..... Minneapolis
‡ Hall, Harry B. ..... Minnapolis
Hall, Wendell H. ..... Minneapolis
‡ Hallin, Roger P. ..... Minneapolis
Halpern, Daniel ..... Minneapolis
Hambidge, Gove, Jr. ..... Minneapolis
‡ Hamel, Arnold L. ..... Minneapolis
‡ Hamel, Joseph I. ..... Minneapolis
Hammerstrom, Robert N. ..... Minneapolis
Handler, Seymour ..... Minneapolis
‡ Hannah, Hewitt B. ..... Minneapolis
‡ Hansen, Cyrus O. ..... Minneapolis
†‡ Hansen, Erling W. ..... Hopkins
† Hansen, Olga S. ..... Minneapolis
‡ Hansen, Rollin M. ..... Minneapolis
‡ Hanske, Edward A. ..... Minneapolis
† Hanson, Harlow J. ..... Minneapolis
Hanson, Harold B. ..... Minneapolis
‡ Hanson, Harold W. ..... Minneapolis
† Hanson, Henry V. ..... St. Paul
†‡ Hanson, Malcolm B. ..... Osseo
Hanson, Mark C. L. ..... Minneapolis
Hanson, Mildred S. ..... Minneapolis
†‡ Hanson, William A. H. ..... Wayzata
Hanson, William B. ..... Minneapolis
† Harrington, Donald P. ..... Richfield
‡ Harris, Leon D. ..... Minneapolis
‡ Harrison, William C. ..... Minneapolis
‡ Hartig, Paul R. ..... Minneapolis
Hartman, Evelyn E. ..... Minneapolis
‡ Hartwig, John A. ..... Minneapolis
†‡ Harty, Jerome L. ..... Minneapolis
‡ Hass, Frederick M. ..... Minneapolis
‡ Hastings, Donald W. ..... Minneapolis
‡ Hauge, Erling T. ..... Minneapolis
‡ Haugen, George W. ..... Minneapolis
Haugen, John A. ..... Minneapolis
‡ Hauser, Donald C. ..... Minneapolis
† Hauser, George W. ..... Seattle, WA
‡ Havel, Robert J. ..... Minneapolis
‡ Haven, Walter K. ..... Minneapolis
†‡ Hawkinson, Raymond P. ..... Minneapolis
‡ Hay, Lyle J. ..... Minneapolis
‡ Hays, Albert T. ..... Minneapolis
‡ Haywa, E. William ..... Minneapolis
‡ Head, Douglas P. ..... Minneapolis
‡ Hebbel, Robert ..... Minneapolis
‡ Hedrick, William L. ..... Minneapolis
‡ Heinz, John W. ..... Minneapolis
‡ Henrikson, Earl C. ..... Minneapolis
Herbert, Willis L. ..... Minneapolis
‡ Hess, Carroll N. ..... Minneapolis
Hewitt, Marshall I. ..... Minneapolis
Hiatt, John A. ..... Minneapolis
Hickok, David F. ..... Minneapolis
†‡ Hildebrandt, Walter C. ..... Minneapolis
‡ Hilgermann, George O. ..... Minneapolis
‡ Hill, Earl ..... Minneapolis

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Hennepin County Medical Society *(Continued)*

‡ Hill, Elmer M. ..... Minneapolis
‡ Hiller, Bruce H. ..... Minneapolis
‡ Hitchcock, Claude R. ..... Minneapolis
‡ Hodges, Kenneth V. ..... Minneapolis
‡ Hoffert, Henry E. ..... Minneapolis
‡ Hoffman, Roy A. ..... Minneapolis
‡ Hoffman, Walter Lees ..... Minneapolis
‡ Hofmann, Gerald N. ..... Minneapolis
‡ Holmberg, Conrad J. ..... Minneapolis
‡ Holten, David R. ..... Minneapolis
Holzapfel, Fred C. ..... Minneapolis
‡ Hopperstad, J. Jerome ..... Minneapolis
‡ Hoppes, Emerson E. ..... Minneapolis
‡ Horns, Howard L. ..... Minneapolis
Horns, Norman ..... Minneapolis
‡ Horns, Richard C. ..... Minneapolis
‡ Hoseth, Wayne L. ..... Minneapolis
†‡ Houle, Rollin J. ..... New Brighton
Hourigan, Thomas S. ..... Minneapolis
Hovland, Melvin L. ..... Minneapolis
Hovland, Richard D. ..... Minneapolis
‡ Howard, Robert B. ..... Minneapolis
Howard, Solomon E. ..... Minneapolis
‡ Howell, Carter W. ..... Minneapolis
‡ Hoyt, C. Sherman ..... Minneapolis
† Hudson, George E. ..... St. Louis Park
† Huenekens, Edgar J. ..... Minneapolis
‡ Huff, John S. ..... Minneapolis
‡ Hulteng, Donald B. ..... Minneapolis
† Hultkrans, Rudolph E. ..... Minneapolis
‡ Hurr, Maland C. ..... Minneapolis
‡ Hustad, Edward G. ..... Minneapolis
‡ Hymes, Charles ..... Minneapolis

Ide, Arthur W., Jr. ..... Minneapolis
‡ Idstrom, Linneus G. ..... Minneapolis
‡ Indeck, Walter ..... Minneapolis
Ingalls, Edgar G. ..... Minneapolis
Iverslie, Philip C. ..... Minneapolis
Iverson, Eleanor B. ..... Minneapolis
‡ Iverson, Rolf M. ..... Minneapolis

‡ Jackson, J. Albert ..... Minneapolis
Jackson, Richard L. ..... Minneapolis
‡ Jacobson, Leslie W. ..... Minneapolis
‡ Jacobson, Loren J. ..... Minneapolis
Jacobson, Wyman E. ..... St. Louis Park
‡ Jaffe, Manuel O. ..... Minneapolis
‡ Janda, George W., Jr. ..... Minneapolis
‡ Jay, Alan R. ..... Rochester
‡ Jefferies, William L. ..... Minneapolis
Jensen, Nathan K. ..... Minneapolis
Jensen, Paul A. ..... Minneapolis
Jensen, Reynold A. ..... Minnetonka
Jepson, William W. ..... Minneapolis
Jerome, Bourne ..... Minneapolis
Jerome, Elizabeth B. K. ..... Minneapolis
‡ Jeub, Robert P. ..... Minneapolis
Jinkins, Roger E. ..... Minneapolis
† Johanson, Waldemar G., Jr. ..... Dallas, TX
‡ Johnson, Angelo G. ..... Minneapolis
‡ Johnson, Arthur B. ..... Minneapolis
Johnson, Bradley D. ..... Minneapolis
‡ Johnson, David R. ..... Minneapolis
#‡Johnson, Donald A. ..... Minneapolis
Johnson, Edward A. ..... Minneapolis
‡ Johnson, Frank E. ..... Minneapolis
Johnson, Gordon E. ..... Minneapolis
Johnson, Harry A., Jr. ..... Minneapolis
†‡ Johnson, James A. ..... Minneapolis
‡ Johnson, John W. ..... Minneapolis
Johnson, Norman P. ..... Minneapolis
Johnson, Norman Paul ..... St. Paul
‡ Johnson, Norton T. ..... Minneapolis
‡ Johnson, Reinald G. ..... Minneapolis
† Johnson, Reuben A. ..... Minneapolis
‡ Johnson, Richard S. ..... Minneapolis
‡ Johnson, Robert E. ..... Minneapolis
Johnson, Thomas H., Jr. ..... Minneapolis
Johnson, Youbert T. ..... Minneapolis
Johnston, Donald K. ..... Minneapolis
Jones, David G. ..... Minneapolis
†‡ Jones, Herbert W., Jr. ..... Minneapolis
‡ Jones, Richard H. ..... Minneapolis
Jordan, Donald V. ..... Minneapolis
Jorgensen, Harlan ..... Minneapolis
‡ Judd, Allen S. ..... Minneapolis
‡ Judd, Walter H. ..... Washington, DC
Jurdy, Mitchell J. ..... Minneapolis

‡ Kadesky, Harold B. ..... Minneapolis
Kaiser, Harold B. ..... Minneapolis
Kalb, Thomas J. ..... Minneapolis
‡ Kallestad, Leonard L. ..... Wayzata
Kane, Dennis J. ..... Minneapolis
‡ Kane, Morton C. ..... Minneapolis
Kane, William J. ..... Minneapolis
‡ Kaplan, Harold A. ..... Minneapolis
‡ Kaplan, J. Jacob ..... Minneapolis
‡ Karleen, Conrad I. ..... Minneapolis
‡ Karlen, Markle ..... Minneapolis
Kasper, Robert E. ..... Excelsior
‡ Katkov, Harold ..... Wayzata
Katz, Beni ..... Minneapolis
†‡ Kelby, Gjert M. ..... Minneapolis
Kelly, Charles F. ..... Minneapolis
‡ Kelly, John C. ..... Minneapolis
‡ Kelly, John P. ..... Minneapolis
‡ Kelly, John T. ..... Minneapolis
Kennedy, Byrl J. ..... Minneapolis
† Kennedy, Claude C. ..... Minneapolis
Kennedy, William R. ..... Minneapolis
*‡ Kerkhof, Arthur C. ..... Minneapolis
Khorsand, Darius ..... Minneapolis
† Kieffer, Stephen A. ..... Minneapolis
Kim, Mark K. ..... Minneapolis
‡ Kimmel, George C. ..... Minneapolis
Kinney, William N. ..... St. Paul
King, Frances W. ..... Minnetonka
†‡ Kinsella, Thomas J. ..... Minneapolis
‡ Kiser, Joseph C. ..... Minneapolis
Kitchen, Clyde K. ..... Minneapolis
Kjellsen, Douglas L. ..... Minneapolis
Klassen, Arthur C. ..... Minneapolis
Kleven, Lowell H. ..... Minneapolis
‡ Knapp, Miland E. ..... Minneapolis
†‡ Knight, Ralph T. ..... Minneapolis
† Knight, Ray R. ..... Minneapolis
Knobloch, William H. ..... Minneapolis
Knowles, Richard A. ..... Coon Rapids
Knudsen, Helen L. ..... Minneapolis
Kohlhase, Robert E. ..... Minneapolis
‡ Kolars, Charles P. ..... Minneapolis
† Koller, Hermann M. ..... Minneapolis
† Koller, Louis R. ..... Minneapolis
‡ Koller, Robert L. ..... Minneapolis
† Kollmorgan, Rodger C. ..... Minneapolis

Hennepin County Medical Society *(Continued)*

Koontz, Peter S. ..... Minneapolis
Koos, Gerald W. ..... Minneapolis
Korchik, John P. ..... Minneapolis
Koropchak, Nickolas ..... Minneapolis
‡ Kostich, Nikola D. ..... Minneapolis
Kottke, Frederic J. ..... Minneapolis
Koucky, Rudolph W. ..... Minneapolis
‡ Kovack, Freeman D. ..... Minneapolis
Kozak, Michael J. ..... Minneapolis
‡ Krafft, Walter E. ..... Minneapolis
‡ Kragh, Lyle V. ..... Minneapolis
† Kramer, Daniel W. ..... Minneapolis
‡ Kremen, Arnold J. ..... Minneapolis
Krieser, Albert E. ..... Minneapolis
Krystosek, Lee A. ..... Minneapolis
†‡ Kucera, Frank J. ..... Hopkins
† Kucera, William J. ..... Santa Barbara, CA
‡ Kump, Warren L. ..... Minneapolis
‡ Kusz, Clarence V. ..... Minneapolis
Kyllo, John E. ..... Minneapolis

LaBree, John W. ..... Minneapolis
‡ Lagaard, Sheldon M. ..... Minneapolis
† Lajoie, John M. ..... Minneapolis
‡ Lamb, H. Douglas ..... Minneapolis
‡ Lang, Leonard A. ..... Minneapolis
Langer, Leonard O., Jr. ..... Minneapolis
Lannon, James B. ..... Minneapolis
†‡ Lapierre, Arthur P. ..... Minneapolis
‡ Larsen, Frank W. ..... Minneapolis
‡ Larson, Arthur K. ..... Minneapolis
‡ Larson, Donald M. ..... Minneapolis
‡ Larson, Ernest J., Jr. ..... Minneapolis
Larson, F. Wilmer ..... Minneapolis
‡ Larson, Lawrence M. ..... Minneapolis
† Larson, Leonard M. ..... Minneapolis
Larson, Loren J. ..... Minneapolis
‡ Larson, Paul N. ..... Minneapolis
‡ Larson, Richard E. ..... Minneapolis
‡ Larson, Roger C. ..... Minneapolis
Larson, Wyllis G. ..... Minneapolis
Latts, Elliot M. ..... Minneapolis
† LaVake, Rae T. ..... Minneapolis
Lawrow, John W. ..... Minneapolis
Lawson, Warren R. ..... Minneapolis
‡ Lawton, James J., Jr. ..... Minneapolis
Laymon, Carl W. ..... Minneapolis
† Leach, Clifford G. ..... Minneapolis
Leavenworth, Richard O., Jr. ..... Minneapolis
‡ Leemhuis, Andrew J. ..... Minneapolis
Lees, David C. ..... Minneapolis
‡ Leiferman, Robert J. ..... Minneapolis
Leighton, John S. ..... Patuxent River, MD
Leinonen, Wendla E. ..... Anoka
‡ Lenz, Bernard W. ..... Minneapolis
‡ Lenz, Oa ..... Minneapolis
†‡ Leonard, Lawrence J. ..... Minneapolis
‡ Leonard, Samuel ..... Minneapolis
Lerner, A. Ross ..... Minneapolis
‡ Leslie, Loren R. ..... Minneapolis
Leslie, W. Robert ..... Minneapolis
Letson, Robert D. ..... Minneapolis
Lester, Theodore H. ..... Minneapolis
† Levitan, Alexander A. ..... Minneapolis
‡ Levine, Howard M. ..... Minneapolis
Lewis, F. Bruce ..... Minneapolis
Lewis, Glenn M., Jr. ..... Minneapolis
‡ Lick, Louis C. ..... Minneapolis
Liebhaber, Henia F. ..... Anoka
‡ Lillehei, Richard C. ..... Minneapolis
‡ Limbeck, Donald A. ..... Minneapolis
Lindall, Arnold W., Jr. ..... Minneapolis
‡ Lindberg, Vernon L. ..... Minneapolis
‡ Lindberg, Winston R. ..... Minneapolis
Lindblom, Maurice L. ..... Minneapolis
Lindeland, Arthur T. ..... Dublin, CA
‡ Lindemann, Charles E. ..... Minneapolis
‡ Linderholm, Bruce E. ..... Minneapolis
‡ Lindgren, Russell C. ..... Minneapolis
†‡ Lindquist, Richard H. ..... Minneapolis
Lindseth, Esten O. ..... Minneapolis
‡ Linner, John H. ..... Minneapolis
†‡ Linner, Paul W. ..... Minneapolis
Lipschultz, Oscar ..... St. Louis Park
Litman, Abraham B. ..... Minneapolis
†‡ Litman, Thomas ..... Minneapolis
† Lloyd, Judson F. ..... Minneapolis
Lober, Paul H. ..... Minneapolis
‡ Locke, Murray S. ..... Minneapolis
Lofsness, Stanley V. ..... Minneapolis
‡ Logothetis, John A. ..... Minneapolis
Loken, Merle K. ..... Minneapolis
‡ Lott, Frederick H. ..... Minneapolis
† Lovett, Beatrice R. ..... Minnetonka
Lowe, Douglass A. ..... Minneapolis
† Lowe, Thomas A. ..... So. St. Paul
Lowry, Elizabeth C. ..... Minneapolis
Lowry, Jeanette K. ..... Minneapolis
Lowry, Paul T. ..... Minneapolis
Lowry, Thomas ..... Minneapolis
Lueck, Wallace W. ..... Minneapolis
‡ Lufkin, Nathaniel H. ..... Minneapolis
‡ Luh, Edwin F. ..... St. Paul
Lund, George W. ..... Minneapolis
Lund, Nancy R. ..... Minneapolis
‡ Lund, Richard R. ..... Minneapolis
† Lundberg, Ruth I. ..... St. Paul
‡ Lundblad, Rodger R. ..... Minneapolis
† Lundblad, Roy A. ..... Minneapolis
Lundblad, Stanley W. ..... Minneapolis
†‡ Lundeberg, Karl R. ..... Minneapolis
Lundquist, Charles B. ..... Minneapolis
‡ Lundquist, Virgil J. P. ..... Minneapolis
‡ Lynch, Michael F. ..... Minneapolis
‡ Lynn, Walter ..... Minneapolis
Lyon, Fred A. ..... Minneapolis
‡ Lyon, John D. ..... Hopkins
†‡ Lysne, Henry ..... Minneapolis
Lysne, Richard B. ..... Minneapolis
‡ Lysyj, Anatol ..... Minneapolis
‡ Lyzenga, Anton G. ..... Minneapolis

McCaffrey, F. John ..... Minneapolis
‡ McCampbell, Malcolm D. ..... Minneapolis
‡ McCannel, Malcolm A. ..... Minneapolis
†‡ McCarthy, Donald ..... Minneapolis
‡ McCormick, Donald P. ..... Minneapolis
† McDaniel, Orianna ..... Minneapolis
‡ McFarland, Arthur H. ..... Minneapolis
McGandy, Robert F. ..... Minneapolis
*† McGeary, George E. ..... North Ft. Myers, FL
‡ McInerny, Maurice W. ..... Minneapolis
McKelvey, John M. ..... Minneapolis
‡ McKenna, James L. ..... Minneapolis
‡ McKenzie, Charles H. ..... Minneapolis
†‡ McKinlay, Chauncey A. ..... Minneapolis

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Hennepin County Medical Society *(Continued)*

McKinlay, Gordon L. ..... Minneapolis
† McKinney, Frank S. ..... Minneapolis
McLaughlin, Byron H. ..... Minneapolis
McMahon, John E. ..... Minneapolis
‡ McMurtrie, William B. ..... Minneapolis
McNeil, John J. ..... Minneapolis
‡ McParland, Felix A., Jr. ..... Minneapolis
†‡ McPheeters, Herman O. ..... Minneapolis
†‡ MacDonald, Daniel A. ..... Minneapolis
‡ MacKinnon, Donald C. ..... Minneapolis
†‡ Mach, Frank B. ..... Minneapolis
‡ Mach, John R. ..... Minneapolis
Macheledt, Neil L. ..... Anoka
‡ Madsen, Donald O. ..... Minneapolis
‡ Maeder, Edward C. ..... Minneapolis
Maeder, Edward C., Jr. ..... St. Paul
Magraw, Richard M. ..... Silver Spring, MD
‡ Mahle, James P. ..... Minneapolis
† Maland, Clarence O. ..... Minneapolis
‡ Malmquist, Carl P. ..... Minneapolis
Mandel, Sheldon L. ..... Minneapolis
Manick, Kenneth P. ..... Minneapolis
‡ Mankey, James C. ..... Minneapolis
Mann, George A. ..... Minneapolis
‡ Manoles, Ellias N. ..... Minneapolis
‡ MarCia, Alfred M. ..... Minneapolis
‡ Mark, Aaron L. ..... Minneapolis
Mark, Merle S. ..... Minneapolis
‡ Marking, George H. ..... Minneapolis
Markland, Colin ..... Minneapolis
Markovitz, Jack M. ..... Minneapolis
Marte, Egon ..... Minneapolis
‡ Martin, Frank E. ..... Minneapolis
‡ Martin, George R. ..... Minneapolis
Martinson, Carl J. ..... Wayzata
Martinson, Elmer J. ..... Wayzata
‡ Maslansky, Robert A. ..... Minneapolis
‡ Massee, Joseph S. ..... Minneapolis
‡ Mattson, Hamlin A. N. ..... Minneapolis
Maunder, John B. ..... Minneapolis
† Maxeiner, Stanley R. ..... Minneapolis
‡ Maxeiner, S. R., Jr. ..... Minneapolis
‡ Mayberg, Donald M. ..... Minneapolis
Meany, Thomas J. ..... Minneapolis
Mecklenburg, Fred E. ..... Minneapolis
‡ Meeker, Henry C. ..... Minneapolis
Meekin, Patrick C. ..... Minneapolis
‡ Meller, Robert L. ..... Minneapolis
‡ Mensheha, Nicholas M. ..... Minneapolis
‡ Merner, Thomas B. ..... Minneapolis
† Merrick, Charlotte T. ..... St. Paul
Messenheimer, Myron G. ..... Minneapolis
‡ Metz, Donald D. ..... Minneapolis
‡ Meyer, Alvin J. ..... Minneapolis
† Meyer, E. Lawrence ..... Winona
† Michael, Joseph C. ..... Minneapolis
†‡ Michel, Henry H. ..... Minneapolis
† Michelson, Henry E. ..... Minneapolis
† Mickelson, Emma F. (Fronk) ..... Minneapolis
Middlebrook, John E. ..... Minneapolis
† Miller, Charles H., III ..... Minneapolis
† Miller, Gerald J. ..... Minneapolis
Miller, H. Dawes ..... Minneapolis
‡ Miller, Harold E. ..... Minneapolis
‡ Miller, Hugo E. ..... Minneapolis
‡ Miller, J. Carleton ..... Minneapolis
Miller, William P. ..... Minneapolis
‡ Millett, D. Keith ..... Minneapolis
‡ Milton, John S. ..... Minneapolis
‡ Minder, John G. ..... Minneapolis
Minsky, Armen A. ..... Minneapolis
‡ Mitby, Irvin L. ..... Minneapolis
‡ Mitchell, Berton D. ..... Minneapolis
Mitchell, Edward C. ..... Minneapolis
Mitchell, John S. ..... Seoul, Korea
‡ Mitchell, Mancel T. ..... Minneapolis
‡ Mixer, Harry W. ..... Minneapolis
‡ Moe, John H. ..... Minneapolis
Moe, W. Wyatt ..... Minneapolis
‡ Moehn, John T. ..... Minneapolis
Moen, Johannes K. ..... Minneapolis
Mollers, Theodore P. ..... Ft. Snelling
‡ Monson, Einer M. ..... Minneapolis
Monson, Warren A. ..... Minneapolis
† Moore, Irvin H. ..... Hopkins
Moorhead, Marie ..... Minneapolis
‡ Moos, Daniel J. ..... Minneapolis
‡ Moral, Harvey M. ..... Minneapolis
Moran, Leo J. ..... New Brighton
Moriarty, James A. ..... Minneapolis
Moriarty, Joseph D. ..... Coon Rapids
‡ Mork, A. Harold ..... Anoka
‡ Mork, Frank E. ..... Anoka
‡ Mork, Frank E., Jr. ..... Minneapolis
Morrison, Charlotte J. ..... Minneapolis
‡ Mosser, Donn G. ..... Minneapolis
‡ Moyer, Leonard B. ..... Minneapolis
‡ Mulholland, William M. ..... Minneapolis
‡ Mullin, Gerald T., Jr. ..... Minneapolis
‡ Mulvahill, John E. ..... Minneapolis
‡ Munkittrick, Ronald C. ..... Minneapolis
‡ Murphy, Edmund P. ..... Minneapolis
Murray, Elisabeth M. ..... Minneapolis
‡ Muske, Marvin M. ..... Minneapolis
‡ Musty, Nicholas J. ..... Minneapolis
‡ Myers, Jay A. ..... Minneapolis
‡ Myhre, James ..... Minneapolis
Mylrea, Murray J. ..... Minneapolis

‡ Nagobads, Ilgvars J. ..... Minneapolis
Nagobads, V. George ..... Minneapolis
Najarian, John S. ..... Minneapolis
Nash, Eldor E. B. ..... Minneapolis
*‡ Naslund, Ames W. ..... Minneapolis
Nauth, Bernard S. ..... Scottsdale, AZ
†‡ Neal, Joe M. ..... Minneapolis
‡ Neary, Richard P. ..... Minneapolis
† Nelson, Bernette G. ..... Slayton
† Nelson, Bernice A. ..... Minneapolis
Nelson, C. Barton ..... Minneapolis
Nelson, Carleton A. ..... Minneapolis
‡ Nelson, David J. ..... Minneapolis
‡ Nelson, Edward N. ..... Minneapolis
Nelson, Evan L., Jr. ..... Minneapolis
‡ Nelson, George E. ..... Minneapolis
Nelson, Gunard A. ..... Minneapolis
†‡ Nelson, Harvey ..... Pompano Beach, FL
‡ Nelson, Lloyd S. ..... Minneapolis
Nelson, Maxine O. ..... Minneapolis
‡ Nelson, Maynard C. ..... Minneapolis
‡ Nelson, O. L. Norman ..... Minneapolis
‡ Nelson, Wallace I. ..... Minneapolis
‡ Nerenberg, Sidney ..... Minneapolis
‡ Nesset, Lawren B. ..... Minneapolis
‡ Nesset, William D. ..... Minneapolis
Neumann, Roland F. ..... Minneapolis
‡ Neumeister, Charles A. ..... Minneapolis
Neuwirth, Gerardo D. ..... Minneapolis

Hennepin County Medical Society *(Continued)*

Nicholas, S. Scott, Jr. ..... Minneapolis
Nielsen, David J. ..... Minneapolis
‡ Nilsen, John A. ..... Minneapolis
Nolan, Robert K. ..... Brooklyn Center
‡ Noran, Harold H. ..... Minneapolis
‡ Nord, Robert E. ..... Minneapolis
† Nordin, Gustaf T. ..... Kaneohe, HI
*†‡Nordland, Martin ..... Minneapolis
Noren, George R. ..... Minneapolis
‡ Norman, Mark L., Jr. ..... Minneapolis
Norval, Mildred A. ..... Minneapolis
Nuessle, William F. ..... Minneapolis
Nydahl, Bruce C. ..... Minneapolis
‡ Nydahl, Malvin J. ..... Minneapolis

O'Brien, Bruce J. ..... Minneapolis
‡ O'Brien, William A. ..... Minneapolis
† O'Donnell, James E. ..... Minneapolis
O'Neil, Bernerd L. ..... Minneapolis
‡ O'Phelan, E. Harvey ..... Minneapolis
Officer, Charles D. ..... Burnsville
Olavs, Olga ..... Minneapolis
‡ Olfelt, Paul C. ..... Minneapolis
‡ Olsen, E. George ..... Minnetonka
‡ Olsen, Jay R. ..... Minneapolis
‡ Olson, Alton C. ..... Minneapolis
‡ Olson, C. Kent ..... Minneapolis
Olson, Carl J. ..... Minneapolis
‡ Olson, Detlof M. ..... Minneapolis
‡ Olson, Duane C. ..... Minneapolis
Olson, Hardin E. ..... Minneapolis
† Olson, Olaf A. ..... Minneapolis
‡ Olson, Philip A. ..... Minneapolis
‡ Olson, Robert A. ..... Minneapolis
Olson, Robert E. ..... Minneapolis
Olson, Robert W. ..... Minneapolis
Olson, Rolland A. ..... Wayzata
Onstad, Gerald R. ..... Fort Rucker, AL
‡ Opheim, Richard H. ..... Minneapolis
‡ Oppen, E. Gerhard ..... Minneapolis
‡ Oppen, Melvin G. ..... Minnetonka
Opstad, Earl T. ..... Minneapolis
‡ Orbuch, Martin W. ..... Minneapolis
‡ Orkin, Milton ..... Minneapolis
‡ Osterberg, Kenneth A. ..... Minneapolis
Ott, Eugene C. ..... Minneapolis
† Overby, Philip G. ..... Minneapolis
Owen, Richard R. ..... Minneapolis

Paal, Dwain J. ..... Minneapolis
Page, Raymond L. ..... Minneapolis
Paisner, Hyman M. ..... Minneapolis
‡ Palen, Benjamin J. ..... Scottsdale, AZ
‡ Palm, E. Theodore ..... Minneapolis
Papermaster, Ralph ..... Minneapolis
‡ Papermaster, Theodore C. ..... Wayzata
Paparella, Michael M. ..... Minneapolis
Park, Wilford E. ..... Minneapolis
Parod, John D. ..... Minneapolis
‡ Parrott, John C. ..... Minneapolis
‡ Pattee, James J. ..... Minneapolis
Patterson, Paul G. ..... Minneapolis
Paule, William J. ..... Minneapolis
Peake, Janna Z. ..... Minneapolis
‡ Peiper, Warren S. ..... Minneapolis
‡ Peluso, Charles R. ..... Minneapolis
Pennington, Mary ..... Minneapolis
‡ Peper, Martin C. ..... Minneapolis
‡ Perlman, Everett C. ..... Minneapolis
Perlman, Herschel L. ..... St. Louis Park
‡ Peteler, Jennings C. L. ..... Minneapolis
Petersen, Byron D. ..... Minneapolis
‡ Petersen, Deane A. ..... Wayzata
‡ Petersen, Glenn L. ..... Minneapolis
‡ Petersen, William E. ..... Minneapolis
Peterson, Charles A. ..... Minneapolis
Peterson, John A. ..... Minneapolis
Peterson, Oliver H., Jr. ..... Minneapolis
Peterson, Palmer A. ..... Minneapolis
‡ Peterson, Theodore A. ..... Minneapolis
Peterson, W. Henry ..... Minneapolis
† Peterson, Willard C., Sr. ..... Minneapolis
‡ Peterson, Willard C., Jr. ..... Minneapolis
‡ Petit, Julien V. ..... Minneapolis
†‡ Petit, Leon J. ..... Minneapolis
‡ Pewters, John T. ..... Minneapolis
‡ Pfohl, Richard A. ..... Minneapolis
† Phelps, Kenneth A. ..... St. Petersburg, FL
Phelps, Robert D. ..... Minneapolis
Phibbs, Clifford M., Jr. ..... Minneapolis
Pincus, Mitchell ..... Minneapolis
‡ Plasha, Matthew K. ..... Coon Rapids
‡ Plass, Herbert F. R. ..... Minneapolis
Pohl, John F. ..... Minneapolis
Polesky, Herbert F. ..... Minneapolis
Poley, Brooks J. ..... Minneapolis
‡ Pollak, Kurt ..... Minneapolis
‡ Pollock, Anthony J. ..... Edina
‡ Polzak, Jacob A. ..... Minneapolis
Pone, John J. ..... Minneapolis
‡ Popadiuk, Peter ..... Minneapolis
#‡Popowich, John G. ..... Denver, CO
† Poppe, Frederick H. ..... Miami, FL
‡ Potter, Robert B. ..... Minneapolis
*† Pratt, Fred J., Sr. ..... Minneapolis
‡ Pratt, Fred J., Jr. ..... Minneapolis
‡ Prem, Konald A. ..... Minneapolis
‡ Preston, Frank S., Jr. ..... Minneapolis
‡ Price, William E. ..... Minneapolis
Prickman, William E. ..... Minneapolis
‡ Priest, Robert E. ..... Minneapolis
†‡ Prim, Joseph A. ..... Minneapolis
*‡ Proffitt, William E. ..... Minneapolis
‡ Proshek, Lumir C. ..... Minneapolis

‡ Quello, Robert O. B. ..... Minneapolis
Quiggle, Arthur B. ..... Minneapolis
‡ Quist, Henry W., Jr. ..... Minneapolis

‡ Raab, David E. ..... Minneapolis
Racer, Harley J. ..... Minneapolis
Raich, John J. ..... Minneapolis
‡ Raile, Richard B. ..... Minneapolis
Randall, David A. ..... Minneapolis
‡ Ransom, H. Robert ..... Osseo
‡ Ratelle, Alexander E. ..... Minneapolis
Recht, Thomas M. ..... Minneapolis
‡ Reece, Richard L. ..... Minneapolis
Read, Sheldon C. ..... Minneapolis
‡ Regan, John J. ..... Minneapolis
†‡ Regnier, Edward A. ..... Minneapolis
Reichel, Samuel M. ..... Minneapolis
‡ Reif, Harold A. ..... Minneapolis
‡ Reiley, Richard E. ..... Minneapolis
‡ Reiser, Milton P. ..... Minneapolis
† Reller, Carl Raymond, Jr. ..... Minneapolis

Continued on Next Page

Hennepin County Medical Society *(Continued)*

‡ Remole, William D. ..... Minneapolis
‡ Resch, Joseph A. ..... Minneapolis
‡ Reynolds, James ..... Minneapolis
‡ Rholl, Arnold O. ..... Minneapolis
‡ Rice, Carl O. ..... Minneapolis
Rice, Edwin S. ..... Minneapolis
Rice, Fred A. ..... Minneapolis
‡ Richardson, Robert J. ..... Minneapolis
†‡ Richdorf, Lawrence F. ..... Minneapolis
‡ Rieke, W. W. ..... Wayzata
Riley, John D. ..... Minneapolis
Riley, William J. ..... Minneapolis
Riordan, Elsie M. ..... Minneapolis
‡ Ripple, Rudolph J., Jr. ..... Minneapolis
‡ Risch, Ronald E. ..... Minneapolis
‡ Rizer, Dean K. ..... Minneapolis
† Robb, Edwin F. ..... Minneapolis
‡ Robbins, Owen F. ..... Minneapolis
Roberts, Byron H. ..... Minneapolis
‡ Roberts, Lewis J. ..... Minneapolis
‡ Roberts, Stanley W. ..... Minneapolis
Robinson, Cortland O. ..... Minneapolis
‡ Rock, William H. ..... Anoka
‡ Rocknem, Robert E. ..... Minneapolis
Rockwell, Curtiss V. ..... Minneapolis
‡ Rodgers, Richard S. ..... Minneapolis
‡ Rogin, Norton ..... Minneapolis
‡ Rollins, Pat ..... Minnetonka
‡ Romness, Kenneth B. ..... Mound
‡ Rosenbaum, David L. ..... Minneapolis
Rosendahl, Frederick G. ..... Minneapolis
†‡ Rosenfield, Abraham B. ..... Minneapolis
Rosenstein, Hanan J. ..... Minneapolis
Rosenow, John H. ..... Minneapolis
†‡ Rosenwald, Reuben M. ..... Anoka
‡ Rossen, Ralph ..... Minneapolis
‡ Rotenberg, Robert J. ..... Minneapolis
Rotenberg, Samuel ..... Huntington Park, CA
Rothnem, Morris S. ..... Minneapolis
Rubin, Manly ..... Minneapolis
‡ Rucker, Thomas K. ..... Minneapolis
† Rucker, William H. ..... Minneapolis
† Rud, Norman E. ..... Edina
Runquist, Richard K. ..... Cambridge
‡ Russeth, Arthur N. ..... Minneapolis
‡ Rusten, Elmer M. ..... Minneapolis
Rydberg, John S. ..... Minneapolis
Rydburg, Wayne C. ..... Minneapolis
‡ Rydland, Arne D. ..... Minneapolis

‡ St. Cyr, Harry M. ..... Minneapolis
‡ St. Cyr, Kenneth J. ..... Minneapolis
Salchert, John J. ..... Minneapolis
‡ Saliterman, Bernard I. ..... Minneapolis
‡ Salovich, Edward L. ..... Minneapolis
‡ Salovich, Elmer R. ..... Minneapolis
‡ Sanchez, Jose S. ..... Edina
‡ Sandt, Karl E. ..... Minneapolis
‡ Sanfilippo, Sylvester J. ..... Minneapolis
Sartor, Richard ..... Minneapolis
‡ Sayther, Keith D. ..... Minneapolis
‡ Sborov, Abe M. ..... Minneapolis
Scallen, Raymond W. ..... Minneapolis
Scanlan, Patrick J. ..... Minneapolis
Schaar, Frances E. ..... Minneapolis
Schaefer, Wesley G. ..... Minneapolis
Schaffhausen, Irwin F. ..... Minneapolis
Schaffhausen, Mildred ..... Minneapolis
*† Scheldrup, Nicolay H. ..... Minneapolis
‡ Scherer, L. Raymond ..... Minneapolis
Scherling, Sidney S. ..... Minneapolis
Schiele, Burtrum C. ..... Minneapolis
Schissel, Gregory A. ..... Minneapolis
‡ Schmidt, W. Robert ..... Minneapolis
† Schmitt, Samuel C. ..... Fallbrook, CA
Schneck, Jack I. ..... Minneapolis
Schoening, Herbert A. ..... Minneapolis
Schoenwetter, William F. ..... Phoenixville, PA
Schottler, Jerry L. ..... Fort Leonard Wood, MO
Schottler, Max E. ..... Minneapolis
† Schroeder, Albert J. ..... Minneapolis
‡ Schultz, Alvin L. ..... Minneapolis
Schultz, Earl A. ..... Minneapolis
‡ Schultz, J. Harold ..... Minneapolis
‡ Schultz, Peter J. ..... Minneapolis
Schultz, Robert J. ..... Minneapolis
‡ Schulze, William M. ..... Minneapolis
‡ Schumacher, John W. ..... Minneapolis
Schwartz, E. Robert ..... Minneapolis
*†‡Schwartz, Virgil J. ..... Minneapolis
‡ Scott, Horace G. ..... Minneapolis
Scott, Robert H. ..... Clinton Sherman AFB, OK
† Seaberg, John A. ..... Pequot Lakes
Seay, James E., III ..... Minneapolis
Segal, Edward L. ..... Minneapolis
‡ Segal, Martin A. ..... Minneapolis
† Seham, Max ..... St. Paul
Seibel, David I. ..... Minneapolis
Seifert, Gregory L. ..... Excelsior
‡ Seifert, Milton H. ..... Excelsior
‡ Seifert, Milton H., Jr. ..... Excelsior
Semba, Thomas ..... Minneapolis
‡ Semsch, Robert D. ..... Wayzata
Severseike, Odean M. ..... Minneapolis
‡ Shandorf, James F. ..... Minneapolis
† Shaperman, Eva P. ..... La Mesa, CA
Shapiro, Irving ..... Minneapolis
Shapiro, Sidney K. ..... Minneapolis
Shapiro, Stanley W. ..... Minneapolis
‡ Shattuck, Clark A. ..... Minneapolis
‡ Shaw, Howard A. ..... Minneapolis
Shea, Andrew W. ..... Minneapolis
Shemesh, Alvin ..... Minneapolis
‡ Sher, Lewis ..... Minneapolis
‡ Sherman, Lloyd F. ..... Minneapolis
*‡ Sherman, Morris H. ..... Minneapolis
† Shillington, Maurice A. ..... Ft. Lauderdale, FL
Sholler, Lawrence J. ..... Minneapolis
‡ Shragg, Robert I. ..... Minneapolis
‡ Shronts, John F. ..... Minneapolis
Sidell, Franklin D. ..... Minneapolis
Siegmann, William C. ..... Minneapolis
‡ Sigel, Melvin E. ..... Minneapolis
‡ Silas, Ralph M. ..... Minneapolis
Silver, John D. ..... Minneapolis
Silverstein, Paul M. ..... Minneapolis
‡ Simmons, Richard K. ..... Minneapolis
Simo, Kathleen Kay ..... Minneapolis
‡ Simonson, Donald B. ..... Minneapolis
† Simpson, Ellery De W. ..... Phoenix, AZ
‡ Sinykin, Melvin B. ..... Minneapolis
‡ Sipe, James W. ..... Coon Rapids
‡ Skjold, Arthur C. ..... Minneapolis
Slosser, Gaius, J., II ..... Ft. Knox, KY
Smiley, John T. ..... Minneapolis
‡ Smisek, Frank M. ..... Minneapolis
† Smith, Adam M. ..... Minneapolis

Hennepin County Medical Society *(Continued)*

‡ Smith, Archie M. ..... Minneapolis
Smith, Barlow ..... Minneapolis
‡ Smith, Baxter A., Jr. ..... Minneapolis
‡ Smith, Graham G. ..... Minneapolis
‡ Smith, John E. ..... Minneapolis
Smith, Nadine G. ..... Minneapolis
‡ Smith, Theodore S. ..... Minneapolis
‡ Soderlind, Ragnar T. ..... Minneapolis
‡ Soiseth, Robert P. ..... Minneapolis
‡ Solhaug, Samuel B., Jr. ..... Minneapolis
Soll, Donald J. ..... Minneapolis
‡ Solvason, Harold M. ..... Minneapolis
Spain, W. Thomas ..... Evansville, IN
‡ Spano, Joseph P. ..... Minneapolis
‡ Spencer, Bernard J. ..... Minneapolis
‡ Spencer, David L. ..... Anoka
‡ Spink, Wesley W. ..... Minneapolis
‡ Sponsel, Kenath H. ..... Minneapolis
‡ Stahr, Aubrey C. ..... Hopkins
† Stanford, Charles E. ..... Boynton Beach, FL
† Stanley, Court R. ..... Minneapolis
‡ Staub, Henry P. ..... Minneapolis
Steidl, Richard M. ..... Minneapolis
‡ Stelter, Lloyd A. ..... Minneapolis
† Stenstrom, Annette T. ..... Holmes Beach, FL
Stenzel, Donald A. ..... Minneapolis
Stenzel, Joseph A. ..... Minneapolis
‡ Stephens, William E. ..... Minneapolis
Sterrie, Norman A. ..... Minneapolis
† Stewart, Marvin J. ..... Minneapolis
Stewart, Paul B. ..... Minneapolis
‡ Stiegler, Farrell S. ..... Minneapolis
‡ Stoesser, Albert V. ..... Minneapolis
Stolee, Curtis N. ..... Ft. Dauphin, Madagascar
‡ Stoltz, Robert C. ..... Minneapolis
Stone, Norman F. ..... Minneapolis
Stone, Stanley P. ..... Minneapolis
‡ Strait, Herbert S. ..... Minneapolis
Strand, Clarence M. ..... Minneapolis
‡ Streu, Richard E. ..... Minneapolis
‡ Strickler, Jacob H. ..... Minneapolis
Strobel, Jack L. ..... Minneapolis
‡ Strom, Gordon W. ..... Minneapolis
‡ Strom, Robert L. ..... Minneapolis
‡ Stromgren, Delph T. ..... Minneapolis
† Stromme, William B. ..... Minneapolis
Strunk, Clarence A. ..... Minneapolis
‡ Student, Richard E. ..... Minneapolis
‡ Sturges, Robert L. ..... Minneapolis
Subak, Barbara H. ..... Minneapolis
‡ Subby, Walter ..... Minneapolis
Sukov, Marvin ..... Minneapolis
Sulciner, Aurel ..... Minnetonka
‡ Sundberg, A. Bruce ..... Minneapolis
Swaiman, Kenneth F. ..... Minneapolis
‡ Swallen, Thomas O. ..... Minneapolis
‡ Swanson, David A. ..... Minneapolis
Swanson, John O. ..... Minneapolis
‡ Sweetser, Horatio B. ..... Minneapolis
*†‡Sweetser, Theodore H. ..... Minneapolis
‡ Sweetser, Theodore H., Jr. ..... Minneapolis
*†‡Swendseen, Carl G. ..... Minneapolis
‡ Swendseen, Carl J. ..... Minneapolis
† Swenson, James D. ..... Edina
‡ Swenson, Richard W. ..... Minneapolis
Swift, Dean C. ..... Minneapolis
Symchych, Boris E. ..... Minneapolis
‡ Tam, Ernest C. ..... Minneapolis
‡ Tambornino, Joseph M. ..... Minneapolis
‡ Tanaka, Shin ..... Minneapolis
‡ Tangen, George V. ..... Minneapolis
† Taylor, Joseph H. ..... Ft. Lauderdale, FL
*‡ Taylor, William E. ..... Minneapolis
‡ Tchou, Mien-Fa ..... Minneapolis
‡ Tenner, Robert J. ..... Minneapolis
‡ Teska, Byron A. ..... Minneapolis
‡ Teynor, Joseph W. ..... Minneapolis
Thelemann, Arthur R., Jr. ..... Minneapolis
Theobalt, Inge M. ..... Minneapolis
‡ Thomas, William H. ..... Minnetonka
Thomasson, Robert D. ..... Minneapolis
Thomes, A. Boyd ..... Minneapolis
Thompson, Arthur ..... Minneapolis
‡ Thorson, Stuart V. ..... Minneapolis
‡ Thysell, Desmond M. ..... Minneapolis
‡ Titrud, Leonard A. ..... Minneapolis
Tobin, John A. ..... Minneapolis
Tobin, John D. ..... Minneapolis
Torres, Fernando ..... Minneapolis
Town, Louise A. ..... Minneapolis
‡ Townes, C. Dwight, Jr. ..... Minneapolis
Trach, Benedict B. ..... Minneapolis
Treat, William A. ..... Minneapolis
‡ Trost, Francis J. ..... Minneapolis
‡ Trow, James E. ..... Minneapolis
Trow, William H. ..... Hopkins
Tsai, Shih Hao ..... Minnetonka
‡ Tucker, Richard C. ..... Minneapolis
‡ Tudor, Richard B. ..... Minneapolis
Turkbas, Nejat ..... St. Paul
‡ Twidwell, Joseph E. ..... Minneapolis

‡ Ulvestad, Harold S. ..... Minneapolis
‡ Utendorfer, Robert W. ..... Minneapolis

Vaaler, Robert T. ..... Minneapolis
‡ Valgemae, Romil ..... Minneapolis
Van Oppen, Dirk J. A. ..... Minneapolis
‡ Vellek, Donald G. ..... Minneapolis
Vennes, Jack A. ..... Minneapolis
Vik, A. Elliott ..... Minneapolis
‡ Von Drashek, Stanley C. ..... Minneapolis
Vorlicky, Loren N. ..... Minneapolis
* Vroman, Donald C. ..... Omaha, NB

Wagner, Christian J. ..... Minneapolis
‡ Wagner, Robert M. ..... Minneapolis
† Waldron, Carl W. ..... Scottsdale, AZ
‡ Waldron, John F. ..... Minneapolis
‡ Wall, Carl R. ..... Minneapolis
Wallinga, Jack V. ..... Minneapolis
†‡ Walonick, Albert L. ..... Hopkins
Walsh, Francis M. ..... Minneapolis
Walsh, John G. ..... Silver Spring, MD
Wang, Yang ..... Minneapolis
‡ Wagensteen, Owen H. ..... Minneapolis
‡ Warren, John W. ..... Minneapolis
‡ Watson, C. Gordon ..... Minneapolis
Watson, Cecil J. ..... Minneapolis
Wattenberg, Lee W. ..... Minneapolis
‡ Weatherhead, Donald S. P. ..... Minneapolis
‡ Webb, Edgar A. ..... Minneapolis
‡ Webber, Richard J. ..... Minneapolis
‡ Weber, Lowell W. ..... Minneapolis
‡ Weisberg, Rapheal J. ..... Minneapolis
Weisel, Mary R. ..... Minneapolis
‡ Wendland, John P. ..... Minneapolis
Werner, George ..... Minneapolis

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Hennepin County Medical Society *(Continued)*

‡ Wesolowski, Stanley ..... Minneapolis
† West, Catherine C. ..... Edina
Wester, Mary Sue ..... Minneapolis
‡ Westgate, Hugh D. ..... Minneapolis
Wetherby, Macnider ..... Minneapolis
Wetherby, Macnider, Jr. ..... Minneapolis
Wethington, Joseph F. ..... Coon Rapids
‡ Wett, Richard J. ..... Minneapolis
Wexler, Harold M. ..... Minneapolis
‡ Wheeler, Robert W. ..... Minneapolis
Whitacre, John C., II ..... Minneapolis
White, Asher A. ..... Minneapolis
† White, Willard D. ..... Minneapolis
‡ Whitesell, Lloyd A. ..... Minneapolis
Whiting, F. Douglas ..... St. Paul
‡ Widen, Wilford F. ..... Minneapolis
Wigdahl, Luther O. ..... Minneapolis
‡ Wilcox, William A. ..... Minneapolis
Wild, John J. ..... Minneapolis
† Wilder, Kenneth W. ..... Minneapolis
† Wilder, Robert L. ..... Minneapolis
† Wilder, Russell M., Jr. ..... Topeka, KS
‡ Wilder, Walter L. ..... Minneapolis
‡ Wilken, Paul A. ..... Minneapolis
Wilkowski, Conrad J. ..... Minneapolis
‡ Williams, Henry L. ..... Minneapolis
‡ Williams, Paul A. ..... Minneapolis
‡ Williams, Richard E. ..... Robbinsdale
Wilson, John A. ..... Minneapolis
‡ Wilson, Robert E. ..... Minneapolis
‡ Wilson, Thomas M., Jr. ..... Minneapolis
Winchell, Paul ..... Minneapolis
† Winther, Nora M. C. ..... Columbus, OH
‡ Wippermann, Frederic F. ..... Minneapolis
‡ Wisiol, Erich S. ..... Minneapolis
Wisness, Osmund A. ..... Savage
Woellner, Richard C. ..... Minneapolis
†‡ Wohlrabe, Arthur A. ..... Minneapolis
‡ Wohlrabe, A. Cabot ..... Minneapolis
‡ Wohlrabe, Robert G. ..... Minneapolis
Wolter, Fred H. ..... Minneapolis
Woodley, Donald W. ..... Minneapolis
Worrell, Philip J. ..... Minneapolis
‡ Woyda, William C. ..... Minneapolis
‡ Wright, Donald L. ..... Minneapolis
Wright, Francis S. ..... Minneapolis
‡ Wright, William S. ..... Minneapolis
‡ Wuest, Frederick C. ..... Wayzata
† Wynne, Herbert M. N. ..... Minneapolis
Yeager, Terrell F. ..... Anoka
‡ Yelle, Matthew D. ..... Anoka
‡ Ylvisaker, Ragnvald S. ..... Minneapolis
Yonehiro, Earl G. ..... Minneapolis
Young, Ronald C. ..... Minneapolis
† Yue, Wen Y. ..... Minneapolis
Zahrendt, O. Lewis ..... Minneapolis
Zak, Solomon J. ..... Minneapolis
‡ Zarling, V. Richard ..... Minneapolis
‡ Zaworski, Leo A. ..... Minneapolis
‡ Zelickson, Alvin S. ..... Minneapolis
† Zemmers, Robert M. ..... Minneapolis
Zierold, Arthur A. ..... Minneapolis
‡ Zinn, Charles W. ..... Wayzata
‡ Zinter, Ferdinand A. ..... Minneapolis

KANDIYOHI-SWIFT-MEEKER COUNTY MEDICAL SOCIETY

Kandiyohi, Swift and Meeker Counties
Regular meetings, third Thursday of each month
Annual meeting in November
Number of members 59

PRESIDENT
Ruchie, Warren H. ..... Willmar
SECRETARY
Kvale, James N. ..... Atwater
‡ Allison, David D. ..... Litchfield
† Anderson, Richard E. ..... Willmar
‡ Bosland, Howard G. ..... Willmar
Chunn, Stanley S. ..... Willmar
Danielson, Lennox ..... Litchfield
‡ Dille, Donald E. ..... Litchfield
‡ Docksey, John W. ..... Willmar
Dunstan, Paul L. ..... Willmar
Eberley, Tobe S. ..... Benson
Eichelberger, Dale L. ..... Willmar
‡ Ellinger, Albert J. ..... Willmar
Fedor, Robert D. ..... Litchfield
† Frederickson, Alice C. ..... Willmar
Gaebe, Milton B. ..... Clara City
† Giere, Silas W. ..... Benson
‡ Gilman, Lloyd C. ..... Willmar
Griffin, Richard P. ..... Benson
‡ Guy, Jack A. ..... New London
Hazen, Richard W. ..... Willmar
‡ Hinderaker, Harris P. ..... Willmar
‡ Hinz, Walter E. ..... Willmar
‡ Hodapp, Robert V. ..... Willmar
Houts, Joseph C. ..... Dassel
Jacobs, Douglas L. ..... Willmar
Johnson, Daniel A. ..... Litchfield
‡ Johnson, Marvin W. ..... Dassel
‡ Kaufman, Edward J. ..... Appleton
Kvale, James N. ..... Atwater
Larrabee, Walter F., Jr. ..... Willmar
Leitch, Cecil M. ..... Litchfield
McAfee, David K. ..... Willmar
McCarthy, Austin M. ..... Willmar
Macklin, William E. ..... Litchfield
Mattson, Donald S. ..... Willmar
‡ Meinert, John K. ..... Willmar
‡ Michels, Roger P. ..... Willmar
‡ Munneke, Lyle ..... Clara City
‡ Nelson, Robert H. ..... Benson
Nolen, William A. ..... Litchfield
‡ Olson, Gregory M. ..... Litchfield
‡ Opsahl, Lawrence J. ..... Willmar
Petersen, Donald H. ..... Willmar
‡ Peterson, Willard ..... Willmar
*† Porter, Oliver M. ..... Minneapolis
‡ Proeschel, Ray K. ..... Willmar
Reid, William O. ..... Willmar
#‡Robinson, William W. ..... Agana, Guam

Kandiyohi—Swift—Meeker County Medical Society
(Continued)

‡ Rorem, Joseph A. ..... Appleton
‡ Ruchie, Warren H. ..... Willmar
‡ Ruhe, Albert ..... Willmar
Rygh, Harold N. ..... Atwater
Salter, William M. ..... Willmar
Schnell, Frederick S. ..... Litchfield
Skaife, William F. ..... Benson
Smith, Lloyd A. ..... Willmar
†‡ Solsem, Frederick N. S. ..... Spicer
‡ Thompson, Russell A. ..... Willmar
‡ Wagner, Norman W. ..... Benson
Wilmot, Cecil A. ..... Litchfield
Wilmot, Harold E. ..... Litchfield

LYON-LINCOLN COUNTY MEDICAL SOCIETY

Lyon and Lincoln Counties
Regular meetings, 6 meetings—Spring and Fall
Annual meeting fourth Tuesday in October
Number of members 23

PRESIDENT
Monson, Leonard J. ..... Canby
SECRETARY
Boyum, Allan J. ..... Marshall
Bosley, Patrick ..... Balaton
‡ Boyum, Allan J. ..... Marshall
‡ Eckdale, John E. ..... Marshall
* Ferguson, William C. ..... Walnut Grove
†‡ Ford, Burton C. ..... Marshall
‡ Hedenstrom, Philip C. ..... Marshall
*† Hoidale, Andrew D. ..... Tracy
Johnson, C. Percy ..... Tyler
Johnston, Bemis H. ..... Eatontown, NJ
† Kreuzer, Titus C. ..... Ft. Snelling
‡ Lee, Norman J. ..... Tracy
‡ Monson, Leonard J. ..... Canby
‡ Mueller, LeRoy E. ..... Hendricks
‡ Muesing, Mark A. ..... Tyler
‡ Murphy, Joseph E. ..... Marshall
‡ Myers, John W. ..... Canby
‡ Olson, Robert T. ..... Canby
‡ Peterson, Kenneth A. ..... Marshall
† Rohrer, Christian A. ..... Madison Lake
Stover, Laddie E. ..... Marshall
#‡Sutherland, John E. ..... Indianhead, MD
‡ Taintor, Ronald W. ..... Marshall
‡ Thompson, Carl O. ..... Hendricks
*† Vadheim, Alfred L. ..... Brookings, SD
† Workman, Warner G. ..... Tracy
† Yaeger, Wilbert W. ..... Torrance, CA

McLEOD COUNTY MEDICAL SOCIETY

McLeod County
Regular meetings, third Thursday of each month
Annual meeting, December
Number of members 19 as of December 31, 1967

PRESIDENT
Peterson, Kenneth H. ..... Hutchinson
SECRETARY
Smith, George R. ..... Hutchinson
‡ Blackwell, Leonard H. ..... Hutchinson
‡ Bretzke, Carl O. ..... Hutchinson
Carroll, John J. ..... Winsted
‡ Griebie, Grant L. ..... Hutchinson
‡ Huebert, Dan W. ..... Hutchinson
‡ Jensen, Alvin M. ..... Brownton
#‡Kapsner, Adrian L. ..... Minneapolis
‡ Lippmann, Elmer W. ..... Hutchinson
‡ McCoy, Donald E. ..... Glencoe
‡ McNeil, Maurice R. ..... Glencoe
‡ Navratil, Donald R. ..... Glencoe
‡ Neumaier, Arthur ..... Glencoe
‡ Ohmann, Ronald ..... Glencoe
‡ Peterson, Kenneth H. ..... Hutchinson
‡ Selmo, Joseph D. ..... Norwood
‡ Smith, George R. ..... Hutchinson
‡ Smyth, John J. ..... Lester Prairie
Stifter, A. J. ..... Winsted
‡ Truesdale, Clark W. ..... Glencoe

MOWER COUNTY MEDICAL SOCIETY

Mower County
Regular meetings, last Friday of the month
Annual meeting, November
Number of members 41

PRESIDENT
Christian, William L. ..... Austin
SECRETARY
Todd, John C. ..... Austin
‡ Anderson, David P., Jr. ..... Austin
‡ Anderson, Harold J. ..... Austin
‡ Barber, Tracy E. ..... Austin
‡ Christian, William L. ..... Austin
‡ Cronwell, Bernhard J. ..... Austin
Elliott, Harold J. ..... Hayfield
‡ Hagen, John D. ..... Austin
*† Havens, John G. W. ..... Minneapolis
† Hertel, Garfield E. ..... McAllen, TX
‡ Hesla, Inman A. ..... Austin
‡ Isele, Reginald H. ..... Austin

Continued on Next Page

Mower County Medical Society *(Continued)*

† Leck, Paul C. ..... Palm Desert, CA
†‡ Lommen, Peter A. ..... Austin
Lommen, Peter A., Jr. ..... Austin
† McKenna, Jay K. ..... LaJolla, CA
‡ Mathers, John E. ..... Austin
‡ Miller, Herman ..... Austin
‡ Mlinar, Joseph P. ..... Austin
† Morse, Morton P. ..... LeRoy
Morse, Roger D. ..... LeRoy
‡ Muchow, Gene C. ..... Austin
‡ Nesse, James A. ..... Austin
‡ O'Rourke, William J. ..... Austin
‡ Patten, John C. ..... Austin
Pesonen, Clifford A. ..... Austin
‡ Peterson, Stanley C. ..... Austin
‡ Roberts, George A. ..... Austin
† Robertson, Paul A. ..... Austin
‡ Rosenthal, F. Harold ..... Austin
Schneider, Paul J. ..... Adams
Seery, Thomas M. ..... Austin
† Smythe, Gwendolyn S. ..... Austin
‡ Smythe, Lowell J. ..... Austin
Stahl, G. W. ..... Austin
‡ Taufic, Mansur ..... Austin
† Thomson, James M. ..... Austin
‡ Todd, John C. ..... Austin
Twiggs, Leo F. ..... Austin
Van Cleve, H. P., Jr. ..... Austin
‡ Wright, Robert R. ..... Austin

NICOLLET-LE SUEUR COUNTY MEDICAL SOCIETY

Nicollet and LeSueur Counties
Regular meetings, first Monday of even months
Annual meeting, December
Number of members 23

PRESIDENT
Walden, A. Don ..... LeSueur
SECRETARY
Engstrom, George E. ..... St. Peter
‡ Anderson, Jo E. ..... LeSueur
† Branham, Donald S. ..... Hastings
Brink, Donald ..... St. Peter
*‡ Curtis, Rauen A. ..... Le Center
‡ Engstrom, George E. ..... St. Peter
† Ericson, Swan ..... Los Angeles, CA
Gislason, Solveig T. ..... Edina
‡ Grimes, Burton P. ..... St. Peter
Haes, Julius E. ..... St. Peter
‡ Hiniker, Peter J. ..... St. Peter
Koskela, L. E. ..... St. Peter
Larson, Milo H. ..... St. Peter
‡ Lenander, Mellvin E. L. ..... St. Peter
‡ Olmanson, Edmund G. ..... St. Peter
‡ Olmanson, M. Donald ..... St. Peter
‡ Olmanson, Vern ..... St. Peter
† Sauer, Jean C. ..... Ft. Snelling
‡ Sheppard, Charles G. ..... St. Peter
‡ Sjostrom, Lawrence E. ..... St. Peter
‡ Sonnesyn, Nels N. ..... LeSueur
‡ Strathern, Carleton S. ..... St. Peter
Thompson, A. Henry ..... St. Peter
‡ Walden, A. Don ..... LeSueur
Wohlrabe, Clarence F. ..... North Mankato

PARK REGION DISTRICT AND COUNTY MEDICAL SOCIETY

Douglas, Grant, Otter Tail and Wilkin Counties
Regular meetings, March, June, September and December
Annual meeting, December
Number of members 60

PRESIDENT
Clifford, George W. ..... Alexandria
SECRETARY
Orandi, Ahmad ..... Fergus Falls
† Arndt, Harry W. ..... Detroit Lakes
Baker, Jeannette L. ..... Fergus Falls
Baker, Norman H. ..... Fergus Falls
‡ Bateman, Clarence V. ..... Fergus Falls
Boline, Clifford A. ..... Battle Lake
‡ Cain, James H. ..... Alexandria
‡ Carlson, Carl E. ..... Alexandria
Carlson, Homer J. ..... Pelican Rapids
Clifford, George W. ..... Alexandria
Colman, Edward L. ..... Fergus Falls
‡ Daehlin, Rolf ..... Fergus Falls
Doms, Vernon A. ..... Elbow Lake
Emerson, Edwin S. ..... Osakis
‡ Estrem, Ralph L. ..... Fergus Falls
‡ Estrem, Robert D. ..... Fergus Falls
Geiser, Peter M. ..... Alexandria
‡ Hanson, Everett C. ..... New York Mills
‡ Heegaard, William G. ..... Alexandria
‡ Helseth, Hovald K. ..... Fergus Falls
‡ Hom, Leong Y. W. ..... Fergus Falls
† Houkom, Bjarne ..... Hamilton, MT
‡ Jacobson, Clifford W. ..... Breckenridge
Jorgensen, Edward O. ..... Fergus Falls
‡ Kevern, Jay L. ..... Henning
‡ Kippen, Neil ..... Breckenridge
‡ Korda, Henry A. ..... Pelican Rapids
‡ Kuhlmann, Vernon G. ..... Alexandria
Larson, Dorette W. ..... Fergus Falls
‡ Lewis, Charles W. ..... Henning
† Love, Frederick A. ..... Carlos
Lu, Cheng-en ..... Fergus Falls
Lueders, James ..... Evansville
‡ Lund, Carl J. T. ..... Fergus Falls
† Mortensen, Nels G. ..... St. Paul
‡ Mouritsen, Glenn J. ..... Fergus Falls
‡ Ness, Richard A. ..... Fergus Falls
‡ Nicholson, Richard W. ..... Fergus Falls
O'Brien, Louis T. ..... Breckenridge

Park Region District and County Medical Society
(Continued)

Olson, Frances P. ..... Fergus Falls
‡ Orandi, Ahmad ..... Fergus Falls
Orandi, Mehdi ..... Fergus Falls
† Ostergaard, Erling ..... Elbow Lake
*† Parson, Lester R. ..... Elbow Lake
† Patterson, William L. ..... Fergus Falls
Perkins, Douglass E. ..... Alexandria
Reinhardt, James H. ..... Alexandria
‡ Richter, Paul H. ..... Fergus Falls
‡ Rockwood, Philo H. ..... Fergus Falls
‡ Sanderson, David J. ..... Fergus Falls
Schoeneberger, P. B. ..... Perham
‡ Sethre, Arthur E. ..... Fergus Falls
‡ Shaver, Ward ..... Fergus Falls
Sporre, Knute A. ..... Fergus Falls
Stemsrud, Harold L. ..... Alexandria
‡ Syverson, Leslie A. ..... Fergus Falls
†‡ Tanquist, Edwin J. ..... Alexandria
Tanquist, Edwin J., Jr. ..... Alexandria
‡ Undem, Dale ..... Alexandria
Warner, James J. ..... Perham
Wasson, Loren F. ..... Alexandria
Webb, Alexander ..... Elbow Lake

RAMSEY COUNTY MEDICAL SOCIETY

Ramsey County

Regular meetings, last Monday each month except
June, July and August
Annual meeting in January
Number of members . . ?. .

PRESIDENT
Hollinshead, William H. ..... St. Paul
SECRETARY
Ravits, Harold G. ..... St. Paul
SEC'Y-EXECUTIVE OFFICE
Olson, Mrs. Eleanor ..... St. Paul
‡ Abrams, Alexander, Jr. ..... St. Paul
‡ Adair, Albert F., Jr. ..... St. Paul
Adams, Harold R. ..... St. Paul
‡ Ahrens, Robert M. ..... St. Paul
‡ Albrecht, Raymond ..... St. Paul
‡ Alden, John F. ..... St. Paul
‡ Alton, Donald G. ..... St. Paul
‡ Amerongen, Werner W. ..... St. Paul
‡ Anderson, David W. ..... St. Paul
Anderson, James J. ..... St. Paul
Anderson, Margaret C. ..... St. Paul
‡ Anderson, Richard W. ..... St. Paul
‡ Arny, Frederick P. ..... St. Paul
‡ Arzt, Philip K. ..... St. Paul
Ashmore, Herbert C. ..... St. Paul
‡ Auran, David B. ..... St. Paul
‡ Aurelius, J. Richards ..... St. Paul
‡ Ausman, Duane R. ..... St. Paul
‡ Austrian, Sol ..... St. Paul
‡ Babb, Frank S. ..... St. Paul
Bach, Jerome M. ..... St. Paul
‡ Bah, Merle C. ..... St. Paul
Baker, Chilton R., Jr. ..... St. Paul
‡ Balce, Regino V. ..... St. Paul
Bauer, Eugene L. ..... St. Paul
‡ Beck, Charles J. ..... North St. Paul
Beckman, Donovan L. ..... St. Paul
‡ Beek, Harvey O. ..... St. Paul
‡ Beer, John J. ..... St. Paul
‡ Bellomo, James ..... St. Paul
‡ Belz, Reinmar ..... St. Paul
‡ Benepe, James L. ..... St. Paul
Benthack, Elaine M. ..... Minneapolis
†‡ Bernier, M. J. ..... North St. Paul
†‡ Bernstein, William C. ..... St. Paul
†‡ Bieter, Thomas G. ..... St. Paul
Birkebak, Roland C. ..... St. Paul
Black, Earl J. ..... White Bear Lake
Blackburn, Henry W., Jr. ..... St. Paul
‡ Blomberg, William R. ..... St. Paul
‡ Blumberg, Henry B. ..... St. Paul
† Bock, Rolland A. ..... St. Paul
‡ Bonello, Frank J. ..... St. Paul
† Bouma, Lewis R. ..... St. Paul
† Brainard, John B. ..... St. Paul
*† Bray, Elwyn R. ..... St. Paul
‡ Briggs, John F. ..... St. Paul
‡ Briggs, Thomas G. ..... White Bear Lake
Broadie, Thomas E. ..... St. Paul
†‡ Brodie, Walter D. ..... St. Paul
‡ Broman, Harold R., Jr. ..... North St. Paul
‡ Brown, Christopher J. ..... St. Paul
‡ Brown, Hector M. ..... St. Paul
Brown, James E., Jr. ..... St. Paul
Brown, James P. ..... St. Paul
‡ Brown, John M. ..... St. Paul
‡ Bulinski, Theodore J. ..... St. Paul
‡ Burklund, Edwin C. ..... St. Paul
‡ Burlingame, David A. ..... St. Paul
‡ Burmeister, Richard O. ..... St. Paul
Burns, John M. ..... St. Paul
‡ Burton, J. Richard ..... St. Paul
‡ Bush, Robert P. ..... St. Paul
*† Busher, Herbert H. ..... St. Paul
‡ Byrne, William J. ..... St. Paul
‡ Cain, Clark L. ..... St. Paul
‡ Canine, James L. ..... South St. Paul
‡ Carey, Lewis S. ..... St. Paul
Cedarleaf, Cherry B. ..... White Bear Lake
†‡ Chatterton, Carl C. ..... St. Paul
#‡Cich, John A. ..... West St. Paul
Clark, W. Bruce ..... St. Paul
‡ Cochrane, Byron B. ..... St. Paul
Coddon, Walter D. ..... St. Paul
†‡ Colby, Woodard L. ..... St. Paul
Cole, Wallace H. ..... St. Paul
‡ Coleman, John B. ..... St. Paul
‡ Colton, Roger S. ..... St. Paul
‡ Comfort, Thomas H. ..... Minneapolis
‡ Connolly, Coleman J. ..... St. Paul
‡ Connolly, Joseph P. ..... West St. Paul
† Connor, Charles E. ..... St. Paul
†‡ Cook, C. Kenneth ..... St. Paul
Cooper, Charles C. ..... Moose Lake
† Countryman, Roger S. .....Saratoga, CA
‡ Craig, David M. ..... St. Paul
‡ Cram, Barclay M. ..... St. Paul
Crowley, James H. ..... St. Paul
‡ Crudo, Vincent D. ..... St. Paul

Continued on Next Page

Ramsey County Medical Society *(Continued)*

‡ Crum, Arthur Z. ..... St. Paul
† Crump, James W. ..... St. Paul
‡ Culligan, John A. ..... St. Paul
‡ Culver, Lucian G. ..... St. Paul
‡ Cumming, E. Dale ..... St. Paul
‡ Daly, Alfred E. ..... St. Paul
‡ Davis, Edward V. ..... St. Paul
Davis, Eunice A. ..... St. Paul
‡ Dawson, James R. ..... St. Paul
‡ Decker, Charles H. ..... St. Paul
*†‡Derauf, Benjamin I. ..... St. Paul
‡ Derauf, Donald E. ..... St. Paul
‡ Derechin, William ..... St. Paul
‡ Deters, Donald C. ..... St. Paul
†‡ Dittrich, Raymond J. ..... St. Paul
‡ Dolmage, George H. ..... St. Paul
‡ Dooley, Robert T. ..... St. Paul
‡ Dunn, Robert C. ..... St. Paul
‡ Durkin, John L. ..... St. Paul
Duthoy, Everette J. ..... St. Paul
‡ Duvall, Arndt J., III ..... Minneapolis
‡ Dyrdal, Paul J. ..... St. Paul
‡ Earl, George A. ..... St. Paul
‡ Earl, John R. ..... St. Paul
Edwards, J. Willard ..... St. Paul
‡ Edwards, Jesse E. ..... St. Paul
Edwards, Lloyd G. ..... St. Paul
Edwards, Richard B. ..... St. Paul
‡ Edwards, Thomas J. ..... St. Paul
‡ Eelkema, Herman H. ..... St. Paul
Eginton, Charles T. ..... Fargo, ND
‡ Eilers, Vincent E. ..... St. Paul
Emerson, Edward C. ..... St. Paul
Ellis, Ronald W. ..... St. Paul
‡ Emmons, Robert W. ..... St. Paul
Endress, Edward K. ..... St. Paul
‡ England, Rodney W. ..... St. Paul
‡ Enroth, Oscar E. ..... St. Paul
‡ Erlanson, A. Cornell ..... St. Paul
‡ Ersfeld, Murray P. ..... St. Paul
‡ Farkas, John V. ..... St. Paul
‡ Fee, John G. ..... St. Paul
‡ Felder, Davitt A. ..... St. Paul
‡ Felion, Arthur J. ..... St. Paul
‡ Ferguson, John N. ..... St. Paul
†‡ Fesler, Harold H. ..... Eugene, OR
‡ Fink, Daniel L. ..... St. Paul
‡ Fischer, Robert F. ..... St. Paul
‡ Fisher, Dan W. ..... St. Paul
‡ Flannery, Hubert F. ..... St. Paul
Flom, Reynold P. ..... St. Paul
‡ Flom, Robert S. ..... St. Paul
‡ Flynn, Louis L., Jr. ..... St. Paul
‡ Flynn, Robert A. ..... St. Paul
†‡ Fogarty, Charles W. ..... St. Paul
‡ Fogelberg, Emil J. ..... St. Paul
Forsythe, James R. ..... St. Paul
‡ Fox, LeRoy J. ..... St. Paul
‡ Freeman, Charles D., Jr. ..... St. Paul
Fritz, Wallace L. ..... St. Paul
‡ Froats, Charles W. ..... St. Paul
‡ Frye, Charles W. ..... St. Paul
‡ Fuller, Benjamin F. ..... White Bear Lake
Funke, Joyce L. ..... St. Paul
‡ Gaertner, Frank M. J., Jr. ..... St. Paul
‡ Gaertner, John R. ..... St. Paul
‡ Galligan, John J. ..... St. Paul
‡ Gardner, Walter P. ..... St. Paul
Garrow, Douglas M. ..... St. Paul
Gaute, Svend T. ..... St. Paul
†‡ Gehlen, Joseph N. ..... St. Paul
‡ Geist, Robert W. ..... St. Paul
Gibbs, Edward C. ..... St. Paul
‡ Gilchrist, Milton R. ..... St. Paul
‡ Gillespie, Delmar R. ..... St. Paul
‡ Gilsdorf, Donald A. ..... St. Paul
‡ Gleason, Wallace A. ..... St. Paul
‡ Glenny, William R. ..... St. Paul
‡ Goldberg, Robert J. ..... St. Paul
‡ Goldsmith, Joseph W. ..... St. Paul
Goodman, Ernest ..... St. Paul
Goott, Bernard ..... St. Paul
‡ Govrik, Kalman ..... St. Paul
‡ Greene, Jerry G. ..... St. Paul
Greenough, William G. ..... Dallas, TX
‡ Gretsch, Gerald A. ..... St. Paul
Gridley, John W. ..... Minneapolis
#‡Griffin, Patrick J. ..... Atlanta, GA
Griffin, Thomas M. ..... St. Paul
‡ Gumnit, Robert J. ..... St. Paul
‡ Guthrie, J Cameron ..... St. Paul

‡ Hakanson, Erick Y. ..... St. Paul
‡ Hall, Barnard ..... St. Paul
*†‡Hammes, Ernest M. ..... St. Paul
‡ Hammes, Ernest M., Jr. ..... St. Paul
‡ Hannon, Donald W. ..... St. Paul
Hanton, Edward M. ..... St. Paul
Harmon, Gaius E. ..... St. Paul
‡ Harris, John E. ..... Minneapolis
‡ Harris, Max E. ..... St. Paul
‡ Hartfiel, William F. ..... St. Paul
Hartig, Marjorie ..... St. Paul
‡ Hauser, Charles W. ..... St. Paul
†‡ Hauser, Victor P ..... St. Paul
‡ Hawkinson, Harlan W. ..... St. Paul
‡ Hayes, Albert F. ..... St. Paul
‡ Heck, William W. ..... St. Paul
‡ Hedenstrom, Charles W. ..... St. Paul
† Hedenstrom, Frank G. ..... St. Paul
‡ Hedenstrom, Richard H. ..... St. Paul
Hedlund, Charles J. ..... St. Paul
‡ Heilig, William R. ..... St. Paul
‡ Henderson, Terrance ..... White Bear Lake
† Hengstler, William H. ..... St. Paul
‡ Henke, Wilbert J. ..... St. Paul
‡ Henry, James S. ..... St. Paul
Herman, Samuel M. ..... St. Paul
‡ Herrick, Donald W. ..... St. Paul
†‡ Hetzler, John A. ..... St. Paul
Hilgedick, William R. ..... St. Paul
‡ Hilger, Jerome A. ..... St. Paul
‡ Hilger, John ..... St. Paul
‡ Hilger, Laurence D. ..... St. Paul
‡ Hilker, Marcus D. ..... St. Paul
Hill, Charlotte W. ..... St. Paul
‡ Hinckley, Robert G. ..... White Bear Lake
† Hiniker, Louis P. ..... St. Paul
‡ Ho, Shu Kang ..... St. Paul
‡ Hodgson, Corrin H. ..... St. Paul
Hodgson, Jane E. ..... St. Paul
‡ Hohmann, Albert ..... St. Paul
† Holcomb, O. William ..... St. Paul
‡ Hollinshead, William H. ..... St. Paul
‡ Holt, John E. ..... St. Paul
Hopkins, G. Wendell ..... Minneapolis
‡ Hottinger, George ..... St. Paul
Houlton, William H. ..... St. Paul

Ramsey County Medical Society *(Continued)*

‡ Howe, Newell W. ..... West St. Paul
‡ Hunter, Samuel W. ..... St. Paul
‡ Hurwitz, Milton M. ..... St. Paul
‡ Huseby, Thomas L. ..... St. Paul
‡ Husebye, Kjeld O. ..... St. Paul
*† Ide, Arthur W. ..... St. Paul
‡ Jackson, William C. ..... St. Paul
‡ James, Ellery M. ..... St. Paul
‡ James, John W. ..... St. Paul
Janecek, James, Jr. ..... New Brighton
‡ Janssen, Martin E. ..... St. Paul
Jarvis, Charles W. ..... St. Paul
‡ Jastram, Rupert M. ..... St. Paul
‡ Johanson, Waldemar G. ..... St. Paul
Johnson, Carl E. ..... St. Paul
Johnson, Carolyn A. ..... St. Paul
‡ Johnson, Herbert W. ..... St. Paul
‡ Johnson, Richard J. ..... St. Paul
‡ Johnson, Thomas E. ..... St. Paul
‡ Jorgensen, Donald R. ..... St. Paul
Joseph, Arnold H. ..... St. Paul
Kaplan, David H. ..... Minneapolis
‡ Karon, Everett H. ..... St. Paul
‡ Karon, Irvine M. ..... St. Paul
‡ Kasper, Eugene M. ..... St. Paul
Katz, Louis J. ..... Long Beach, CA
‡ Kelly, Albert C. ..... St. Paul
‡ Kelly, Edward H. ..... St. Paul
Kelly, Helen M. ..... St. Paul
‡ Kelly, Joseph R. ..... St. Paul
‡ Kelsey, Chauncey M. ..... St. Paul
‡ Kenefick, Emmett V. ..... St. Paul
‡ Kenyon, Thomas J. ..... St. Paul
† Kesting, Herman ..... St. Paul
Kleinsasser, Warren L. ..... Farmington
‡ Knutson, Gerhard E. ..... St. Paul
‡ Knutson, Robert C. ..... St. Paul
Kodres, Nina ..... St. Paul
‡ Kosiak, Michael ..... St. Paul
Koza, Donald W. ..... St. Paul
Kraatz, Robert W. ..... St. Paul
‡ Kramer, James D. ..... St. Paul
‡ Krezowski, Thomas K. ..... St. Paul
‡ Kugler, Alex A. ..... St. Paul
‡ Kuske, Albert W. ..... St. Paul
‡ Kusske, Bradley W. ..... St. Paul
‡ Kusske, Douglas R. ..... St. Paul
†‡ Kvam, Lowell ..... St. Paul
Lade, Roswith I. ..... St. Paul
LaFave, James W. ..... St. Paul
‡ Lampert, Ronald M. ..... St. Paul
‡ Lane, Miles I. ..... White Bear Lake
‡ Lannin, Bernard G. ..... St. Paul
‡ Lannin, Donald R. ..... St. Paul
Larkin, John E. ..... St. Paul
Larson, Eva Jane Ostergren ..... St. Paul
‡ Laszewski, Franz Von Zelberschwecht ..... St. Paul
‡ Lawler, Kevin M. ..... St. Paul
Lees, Jack R. ..... St. Paul
Lehman, Donald S. ..... St. Paul
‡ Leick, Richard M. ..... St. Paul
† Leitch, Archibald ..... St. Paul
‡ Leonard, Stanley ..... St. Paul
† Lepak, John A. ..... St. Paul
‡ Lerdahl, Kenneth ..... St. Paul
‡ Lessard, Richard J. ..... St. Paul
Leven, N. Logan ..... St. Paul
‡ Leverenz, Carleton W. ..... St. Paul
‡ Levitan, Leonard H. ..... St. Paul
Levitt, George X. ..... St. Paul
Lewis, Joyce S., Jr. ..... Minneapolis
‡ Lick, Charles L. ..... St. Paul
‡ Lick, William J. ..... St. Paul
‡ Lien, Richard J. ..... St. Paul
† Lightbourn, Edgar L. ..... Hastings
‡ Lilleberg, Norbert J. ..... St. Paul
‡ Lillie, Andrew R. ..... St. Paul
‡ Lindell, Robert E. ..... St. Paul
‡ Lindquist, Max F. ..... South St. Paul
Lippman, Hyman S. ..... St. Paul
Litkewitsch, Helene ..... St. Paul
‡ Loken, Selmer M. ..... St. Paul
Lowe, Alexander D. ..... South St. Paul
† Lowe, Thomas A. ..... South St. Paul
‡ Lufkin, Murray W. ..... St. Paul
‡ Lundholm, Arthur M. ..... Harris
‡ Lunzer, Richard G. ..... St. Paul
‡ Lynch, Francis W. ..... St. Paul
Lynch, Richard P. ..... St. Paul
‡ McCain, Donovan L. ..... St. Paul
‡ McCarthy, Charles J. ..... St. Paul
† McClanahan, Thomas S. ..... White Bear Lake
McClellan, Robert J. ..... St. Paul
McCloud, C. Naumann ..... St. Paul
‡ McEllistrem, Edward J. ..... St. Paul
‡ McEllistrom, Gerald D. ..... St. Paul
‡ McEwan, Alexander ..... St. Paul
‡ McGroarty, Brian J. ..... St. Paul
‡ McHutchinson, Samuel K. ..... St. Paul
McKenzie, Eva E. ..... St. Paul
‡ McNeill, John A. ..... St. Paul
MacCornack, Robert L., Jr. ..... South St. Paul
Mackoff, Sam M. ..... Phoenix, AZ
Madland, Robert S. ..... St Paul
Magary, Victor J., Jr. ..... Ft. Campbell, KY
‡ Malerich, J. Anthony ..... West St. Paul
‡ Manlove, Charles H., Jr. ..... St. Paul
‡ Marta, John B. ..... St. Paul
‡ Martin, Dwight L. ..... St. Paul
†‡ Martineau, Joseph L. ..... St. Paul
Mateo, Guillermo ..... St. Paul
Matthews, James H. ..... Minneapolis
Matus, Richard N. ..... St. Paul
‡ Mazzitello, William F. ..... St. Paul
‡ Mears, Burtis J. ..... St. Paul
‡ Medelman, John P. ..... St. Paul
‡ Melancon, Joseph F. ..... St. Paul
‡ Merrick, Robert L. ..... St. Paul
‡ Michienzi, Leonard J. ..... St. Paul
‡ Miller, Albert G. ..... St. Paul
Miller, Winston R. ..... St. Paul
Miller, Zondal R. ..... St. Paul
‡ Milnar, Frank J. ..... St. Paul
Milroy, Thomas W. ..... Minneapolis
‡ Mishek, Charles J. ..... St. Paul
‡ Mitchell, George S. ..... St. Paul
† Molander, Herbert A. ..... St. Paul
‡ Monahan, Robert H. ..... St. Paul
‡ Mooney, Robert D. ..... St. Paul
Moren, J. Adelaide ..... St. Paul
Moss, Nyel H. ..... St. Paul
‡ Muchmore, Harold G. ..... Oklahoma City,OK
‡ Muller, A. Eugene ..... North St. Paul
Mundahl, Harold R. ..... St. Paul
Murphy, Jack T. ..... St. Paul
‡ Murray, Roger C. ..... St. Paul
‡ Neher, Frederick J. ..... St. Paul

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Ramsey County Medical Society *(Continued)*

‡ Nelson, Delbert R. ..... St. Paul
‡ Nelson, Loren E. ..... St. Paul
‡ Nelson, Louis A. ..... St. Paul
‡ Nelson, Ronald J. ..... St. Paul
Nesvacil, Leon ..... St. Paul
‡ Nichols, Thomas O. ..... St. Paul
‡ Nimlos, Kenneth O. ..... St. Paul
† Nimlos, Lenore O. ..... St. Paul
‡ Norman, David D. ..... St. Paul
Norquist, Joseph L. ..... St. Paul
Nuebel, Charles J. ..... Long Beach, CA
† Nye, Lillian L. ..... St. Paul
O'Brien, Gerald R. ..... Minneapolis
‡ O'Brien, John C. ..... St. Paul
‡ O'Kane, Thomas W. ..... St. Paul
‡ O'Malley, Valentine ..... St. Paul
O'Neill, Nial C. ..... St. Paul
† O'Reilley, Bernard E. ..... Sun City, AZ
Ockuly, Orville E. ..... St. Paul
† Ogden, Warner ..... St. Paul
† Ohage, Justus ..... St. Paul
‡ Olsen, Ralph L. ..... St. Paul
Olson, Barbara F. ..... Minneapolis
‡ Osekowsky, Henry J. ..... St. Paul
†‡ Ostergren, Edward W. ..... St. Paul
Ouellette, Alfred ..... St. Paul
‡ Owens, Frederick M., Jr. ..... St. Paul
‡ Palm, Neil M. ..... St. Paul
‡ Paulson, Elmer C. ..... St. Paul
‡ Paulson, Wallace J. ..... St. Paul
† Pearson, Fritz R. ..... St. Paul
‡ Pearson, Malcolm M. ..... St. Paul
† Pedersen, Arthur H. ..... St. Paul
‡ Perry, John F., Jr. ..... St. Paul
‡ Peterson, Donald H. ..... St. Paul
‡ Peterson, Edward A. ..... St. Paul
‡ Peterson, Harold O. ..... Minneapolis
Peterson, Joel L. E. ..... St. Paul
Peterson, Roy L. ..... White Bear Lake
Phillips, Leonard ..... St. Paul
‡ Plotke, Harry L. ..... St. Paul
Polski, Paul G. ..... South St. Paul
‡ Post, Edmund A. ..... St. Paul
‡ Powers, Robert L. ..... St. Paul
†‡ Prentice, Walter B. ..... St. Paul
‡ Proud, Harry S. ..... St. Paul
Quattlebaum, Frank W. ..... St. Paul
‡ Raaen, Olaf J. ..... St. Paul
Rabcevich, Anatole ..... St. Paul
‡ Ralph, James R. ..... St. Paul
Ramlow, Ralph M. ..... West St. Paul
† Ramsey, Walter R. ..... St. Paul
Rasmussen, Ramby C. ..... St. Paul
‡ Raths, Otto N., Jr. ..... St. Paul
‡ Ravits, Harold G. ..... St. Paul
‡ Rea, Charles E. ..... St. Paul
Redleaf, Paul D. ..... St. Paul
‡ Reid, James W. ..... South St. Paul
‡ Reif, Robert W. ..... White Bear Lake
‡ Richardson, Edward J., Jr. ..... St. Paul
‡ Rick, Paul F. W. ..... St. Paul
‡ Rinkey, Eugene ..... St. Paul
Ripple, Rudolph J. ..... St. Paul
‡ Ritchie, Wallace P. ..... St. Paul
†‡ Ritt, Albert E. ..... St. Paul
‡ Roach, Charles A. ..... St. Paul
‡ Roach, Donald E. ..... St. Paul
‡ Rolig, David H. ..... West St. Paul
‡ Rollie, Orris O. ..... St. Paul
†‡ Rosenthal, Robert ..... St. Paul
Rossing, Robert G. ..... Brooks AFB, TX
‡ Roth, George C. ..... St. Paul
‡ Rowe, Clarence J., Jr. ..... St. Paul
‡ Roy, Philemon C. ..... St. Paul
† Ruhberg, George N. ..... Santa Barbara, CA
‡ Rukavina, John G. ..... St. Paul
‡ Rushay, Arthur J. ..... White Bear Lake
‡ Rusterholz, Alan P. ..... St. Paul
†‡ Ryan, John J. ..... St. Paul
‡ Ryan, Joseph M. ..... St. Paul
‡ Sand, Richard E. ..... St. Paul
‡ Sandkamp, Virgil A. ..... South St. Paul
‡ Sargent, John G. ..... St. Paul
Schaffhausen, George E. ..... St. Paul
‡ Scherek, Jerome J. ..... St. Paul
‡ Schloff, Ivan ..... St. Paul
‡ Schloff, Leonard D. ..... St. Paul
Schmidtke, Reinhardt L. ..... St. Paul
† Schoch, Robert B. J. ..... St. Paul
‡ Schochet, H. Laurence ..... St. Paul
† Schons, Edward ..... Minnetonka Beach
Schossow, George W. ..... White Bear Lake
‡ Schrader, Wayne H. ..... St. Paul
‡ Schroeckenstein, Hugo F. ..... St. Paul
†‡ Schuft, James R. ..... St. Paul
Schwyzer, Marguerite ..... St. Paul
‡ Scott, Eugene E. ..... St. Paul
Sekhon, Mohan S. ..... St. Paul
‡ Sells, Richard J. ..... St. Paul
†‡ Setzer, Hobert J. ..... St. Paul
Severson, Donald R. ..... Minneapolis
† Shannon, William R. ..... Faribault
Shear, Howard H. ..... West St. Paul
‡ Shelander, Marcus I. ..... St. Paul
*† Shellman, John J. ..... Pacific Palisades, CA
Short, Marshall H. ..... St. Paul
Simmonds, Harry N. L. ..... St. Paul
‡ Simons, Leander T. ..... St. Paul
Siegel, Clarence ..... St. Paul
‡ Singer, Benjamin J. ..... St. Paul
‡ Skinner, Abbott ..... St. Paul
† Skinner, Harvey O. ..... St. Paul
‡ Smiley, Donald P. ..... St. Paul
‡ Smisek, Elmer A. ..... St. Paul
Smith, H. Nippert ..... St. Paul
‡ Smith, Vernon D. E. ..... St. Paul
‡ Smith, William T. ..... St. Paul
†‡ Snyder, George W. ..... St. Paul
†‡ Sohlberg, Olof I. ..... St. Paul
‡ Sommerdorf, Vernon L. ..... St. Paul
‡ Sorem, Milton B. ..... St. Paul
‡ Soucheray, Philip H. ..... St. Paul
†‡ Souster, Benjamin B. ..... St. Paul
‡ Sowada, Ernest J. ..... St. Paul
‡ Sperl, Michael P., Jr. ..... St. Paul
‡ Sprafka, Gregory A. ..... St. Paul
‡ Sprafka, Joseph L. ..... St. Paul
‡ Spraitz, Anton F., Jr. ..... St. Paul
Stafne, John G. ..... St. Paul
‡ Stein, Robert L. ..... North St. Paul
‡ Steinberg, Charles L. ..... St. Paul
Stengl, Thomas A. ..... St. Paul
‡ Sterner, Donald C. ..... St. Paul
‡ Sterner, Ernest R. ..... St. Paul
‡ Sterner, John J. ..... St. Paul
‡ Stolee, Thomas A. ..... St. Paul
Straus, Maurice L. ..... St. Paul

Ramsey County Medical Society *(Continued)*

‡ Strem, Edward L. ..... St. Paul
Strickland, Martha J. B. ..... St. Paul
‡ Sturley, Rodney F. ..... St. Paul
‡ Sullivan, W. Albert, Jr. ..... St. Paul
† Swanson, Gerald E. ..... St. Paul
‡ Swanson, Lawrence J. ..... West St. Paul
‡ Swanson, Ralph H. ..... West St. Paul
Swendson, James J. ..... St. Paul
‡ Swenson, Donald B. ..... St. Paul
Tanasichuk, Murray A. ..... St. Paul
‡ Tani, George ..... St. Paul
Tate, Wayne E. ..... South St. Paul
‡ Teeter, Richard R. ..... St. Paul
‡ Teisberg, John E. ..... St. Paul
‡ Thompson, Wayne W. ..... St. Paul
‡ Tiffany, Francis B. ..... St. Paul
‡ Tifft, Cyril R. ..... St. Paul
‡ Tongen, Lyle A. ..... St. Paul
‡ Travis, James S. ..... St. Paul
Tregilgas, Richard B. ..... St. Paul
Trotman, Neil M. ..... St. Paul
Tveten, Omar A. ..... St. Paul
‡ Ubel, Frank A. ..... St. Paul
Vail, David J. ..... St. Paul
Van Bergen, Frederick H. ..... Minneapolis
Van De Riet, Lowell W. ..... St. Paul
‡ Varco, Richard L. ..... St. Paul
‡ Vaughn, C. Gordon ..... St. Paul
Veinbergs, Arnold ..... St. Paul
Veirs, Dean M. ..... Hastings
† Veirs, Ruby J. S. ..... Hastings
†‡ Venables, Alexander E. ..... Ely
Venters, Homer D., Jr. ..... St. Paul
‡ Votel, Thomas W. ..... St. Paul
† Waas, Charles W. ..... St. Paul
‡ Walker, Arthur E. ..... St. Paul
‡ Wall, James O. ..... St. Paul
‡ Walsh, Edward F. ..... St. Paul
‡ Walter, Clarence W. ..... St. Paul
‡ Warner, Clyde M. ..... St. Paul
‡ Warren, Cecil A. ..... St. Paul
Waters, Alvin W. ..... St. Paul
‡ Watson, P. Theodore ..... St. Paul
‡ Watson, William H. A. ..... St. Paul
‡ Watson, William J. ..... Newport
Watz, Clarence E. ..... St. Paul
‡ Webber, Fred L. ..... St. Paul
‡ Wedes, Deno J. ..... St. Paul
Wegleitner, Mark J. ..... Silver Spring, MD
‡ Weigant, Charles E. ..... Fort Snelling
‡ Weis, Benjamin A. ..... St. Paul
‡ Weisberg, Maurice ..... St. Paul
‡ Wenzel, Gilbert P. ..... St. Paul
† Westermeyer, Joseph J. ..... St. Paul
‡ Westover, Darrell E. ..... St. Paul
Wetteland, Thomas F. ..... West St. Paul
‡ Wetzel, Earl V. ..... St. Paul
Wiencke, William M. ..... St. Paul
‡ Wier, G. Thomas ..... St. Paul
†‡ Williams, Clayton K. ..... St. Paul
‡ Williams, George E. ..... St. Paul
‡ Williams, Hugh J. ..... St. Paul
‡ Williams, John A. ..... St. Paul
Williams, Richard A. ..... St. Paul Park
Wilson, Fred B. ..... St. Paul
‡ Winter, Robert B. ..... St. Paul
Wolfson, Justin J. ..... St. Paul
Wolkoff, Hyman J. ..... St. Paul
‡ Woodburn, Robert L. ..... St. Paul
‡ Woolfrey, Bertram F. ..... St. Paul
‡ YaDeau, Richard E. ..... St. Paul
Youngren, Everett R. ..... St. Paul
‡ Zachman, Leo L. ..... St. Paul
‡ Zagaria, James F. ..... St. Paul
‡ Zarling, Max E. ..... St. Paul

RANGE MEDICAL SOCIETY

Koochiching, Itasca and the Northern Portion of
St. Louis County
Regular meetings, fourth Tuesday of the Month
Annual meeting, January
Number of members 105

PRESIDENT

Ahola, Kenneth E. ..... Hibbing

SECRETARY

Kruger, E. Larry ..... Nashwauk

CORRESPONDING SECRETARY

Workman, Mrs. Rae ..... Hibbing
Addy, Edward R. ..... Hibbing
‡ Ahola, Kenneth E. ..... Hibbing
Anderson, Russell H. ..... Virginia
Andre, James C. ..... Grand Rapids
Antonow, Arthur M. ..... Virginia
Baich, Velemir M. ..... Coleraine
Balderson, Robert P. ..... Grand Rapids
Baraga, Anthony R. ..... Hibbing
‡ Barnes, Richard E. ..... Aurora
Bartholdt, H. Peter ..... Cook
† Benell, Otto E. ..... Britt
† Binet, Henry E. ..... Grand Rapids
Birkemeyer, Eugene J. ..... Mountain Home AFB, ID
Bolz, J. Arnold ..... Grand Rapids
Bonner, John L. ..... Grand Rapids
Braun, Ohrmundt C. ..... Grand Rapids
Brende, Joel O. ..... Littlefork
Brockway, Roger W. ..... Grand Rapids
† Cantwell, William F. ..... International Falls
‡ Chermak, Francis G. ..... International Falls
‡ Ciriacy, Edward W. ..... Ely
Cope, Hershel B. ..... Virginia
‡ Coy, Douglas J. ..... Grand Rapids
‡ Crow, George M. ..... International Falls
DeMarais, Lloyd C. ..... Hibbing
Dobler, Manfred G. ..... Ely
‡ Eisenman, Walter ..... Hibbing
Engelstad, Wendell P. ..... Virginia
‡ Erickson, Vernon D. ..... Grand Rapids
Evensta, John B. ..... Grand Rapids
Ewens, George B. ..... Virginia
‡ Ferrell, Clarence R. ..... Grand Rapids
‡ Flynn, Bernard F. ..... Hibbing
‡ French, Bayard T. ..... Hibbing
Friedlieb, Oskar P. ..... Virginia
Gerend, Thomas J. ..... Virginia
Glomstad, Gary B. ..... Deer River
‡ Grahek, Jack P. ..... Ely
‡ Halper, Bernard ..... Hibbing
Halverson, Kermit J. ..... Parkville

Continued on Next Page

Range Medical Society *(Continued)*

‡ Hanover, Ralph D. ..... International Falls
Hansen, Robert E. ..... Hibbing
Hanson, Bernard H. P. ..... Bigfork
‡ Heiam, William C. ..... Cook
Helwig, Karl L. ..... Virginia
Higgs, Paul C. ..... Virginia
Ibrahim, George W. ..... Virginia
† Ireland, Gerald W. ..... St. Paul
Jacobson, Clarence ..... Chisholm
‡ Johnson, Calvin J. ..... Grand Rapids
‡ Johnsrud, Luverne ..... Hibbing
Johnston, H. Wayne ..... Virginia
Karges, Laurel E. ..... Grand Rapids
Karish, Louis J. ..... Grand Rapids
Kelly, Robert T. ..... Grand Rapids
Kiesler, Frank ..... Grand Rapids
‡ Kotchevar, Frank R. ..... Minneapolis
Law, Harrison E. ..... Virginia
Leach, Thomas C. ..... Babbitt
‡ Lee, William C. ..... Hibbing
McClelland, John G. ..... Virginia
McKenna, John J. ..... Virginia
‡ McKenna, Maurice J. ..... Grand Rapids
McQuoid, David W. ..... Littlefork
Martinson, Raymond M. ..... Virginia
‡ Mast, Fredric L. ..... Chisholm
‡ Miettunen, John B. ..... Hibbing
Miks, George M. ..... Aurora
Mock, Charles J. ..... Virginia
‡ Moyer, Richard R. ..... Hibbing
Mueller, Donald R. ..... Grand Rapids
‡ Muller, John J. ..... Hibbing
‡ Murray, Robert A. ..... Hibbing
‡ Neff, Walter S. ..... Britt
Nelimark, Donald R. ..... Virginia
‡ Nollet, Donald J. ..... Hibbing
Owens, Ben P. ..... Hibbing
‡ Paciotti, Vincent J. ..... Hibbing
‡ Parker, Wilbert H. ..... Chisholm
Payne, Richard E. ..... Virginia
Perpich, Irene Kosiak ..... Virginia
Person, Duane F. ..... Virginia
Peterson, Edward N. ..... Virginia
Prlina, Isaac M. ..... Virginia
Reed, Paul ..... Virginia
Richter, David J. ..... Virginia
Roth, Albert H. ..... Deer River
‡ Salter, Reginald A. ..... Virginia
‡ Schirber, Martin J. ..... Grand Rapids
‡ Schweiger, Theodore R. ..... Hibbing
Sher, David A. ..... Virginia
Siegel, John S. ..... Virginia
†‡ Sinamark, Andrew ..... Hibbing
† Sisler, Clifford E. ..... Grand Rapids
Snyker, Omer E. ..... Ely
Stolen, Keith H. ..... Grand Rapids
Summar, M. Thomas ..... Virginia
Swenson, Floyd J. ..... Grand Rapids
Tietz, Charles A. ..... Virginia
‡ Walker, Stuart B. ..... Aurora
‡ Walter, Frederick H. ..... International Falls
Weir, Mathew J. ..... Virginia
‡ Werner, Donald L. ..... Hoyt Lakes
Wheeler, Gilbert S. ..... Virginia
*‡ Will, Charles B. ..... International Falls
Wong, Howard H. ..... Virginia
‡ Woodruff, Whitney ..... Virginia

RED RIVER VALLEY MEDICAL SOCIETY

Kittson, Mahnomen, Marshall, Norman, Pennington, Polk
Red Lake and Roseau Counties
Regular meetings, quarterly
Annual meeting, December
Number of members 43

PRESIDENT

Dagg, Earl ..... Thief River Falls

SECRETARY

Clapp, Hubert D. ..... Crookston
Baab, Robert O. ..... Crookston
‡ Behr, Orlo K. ..... Crookston
‡ Berg, Arnold M. ..... Thief River Falls
† Bratrud, Edward ..... Alexandria
‡ Brown, Glenn W. ..... Halstad
Cameron, John H. ..... Clovis, NM
‡ Clapp, Hubert D. ..... Crookston
Dagg, Earl ..... Thief River Falls
Davidson, Duane J. ..... Thief River Falls
‡ Delmore, John L. ..... Roseau
Dillenburg, Cyril ..... Crookston
†‡ Flancher, Leon H. ..... Detroit Lakes
‡ Foderick, Peter P. ..... Hallock
Herber, Leo ..... Thief River Falls
‡ Hirsh, Stanton ..... Crookston
Holm, Owen W. ..... Crookston
‡ Holmstrom, Carle H. ..... Warren
Hunt, Vincent R. ..... Red Lake Falls
Jensen, John ..... Crookston
‡ Kinkade, Byron R. ..... Ada
‡ Klefstad, Lloyd H. ..... Greenbush
‡ Kostick, William R. ..... Fertile
Leonardson, Peter Y. ..... Red Lake Falls
‡ Loken, Theodore ..... Ada
† Lynde, Orrin G. ..... Los Gatos, CA
Martin, George ..... Thief River Falls
Mercil, Charles B. ..... Mahnomen
‡ Mercil, William F. ..... Crookston
† Nelson, Henry E. ..... Crookston
‡ Oppegaard, C. L. ..... Scottsdale, AZ
#‡ Pollman, Stanley E. ..... Naha, Okinawa
‡ Pumala, Erven E. ..... Warren
‡ Reff, Alan R. ..... Crookston
‡ Roholt, Christian L. ..... McIntosh
Rubin, Jacob S. ..... Crookston
Russ, Homer H. ..... Warroad
Sather, Edgar L. ..... Fosston
‡ Sather, George A. ..... Fosston
‡ Sather, Richard N. ..... Fosston
‡ Sather, Russell O. ..... Crookston
‡ Schnabel, Robert F. ..... Crookston
† Skogerboe, Rudolph B. ..... Minneapolis
Stadem, Clifford ..... Crookston
‡ Stewart, Donald E. ..... Crookston
‡ Thorsgard, Ernest O. ..... Thief River Falls
‡ Uhley, Charles G. ..... Palm Desert, CA
Van Rooy, George T. ..... Thief River Falls
‡ Wikoff, Howard M. ..... Crookston

RENVILLE-REDWOOD COUNTY MEDICAL SOCIETY

Renville and Redwood Counties
Regular meetings, quarterly
Annual meeting, December
Number of members 14

PRESIDENT
Ceplecha, Stanley F. ..... Redwood Falls

SECRETARY
Flinn, James B. ..... Redwood Falls

Alcorn, William J. ..... Wabasso
‡ Anderson, Chester A. ..... Hector
Bingham, George C. ..... Olivia
† Brand, William A. ..... Redwood Falls
‡ Ceplecha, Stanley F. ..... Redwood Falls
*‡ Cosgriff, James A., Sr. ..... Olivia
Cosgriff, James A., Jr. ..... Olivia
† Diessner, A. W. ..... Redwood Falls
‡ Eilers, William B. ..... Redwood Falls
‡ Fawcett, Arthur M. ..... Renville
‡ Flinn, James B. ..... Redwood Falls
‡ Furr, Leo O. ..... Bird Island
‡ Lenz, Joseph R. ..... Morton
‡ Nelson, Glenn E. ..... Fairfax
‡ Strauchler, John ..... Belview

RICE COUNTY MEDICAL SOCIETY

Rice County
Regular meetings, third Tuesday of
January, April, September and November
Annual meeting in November
Number of members 27

PRESIDENT
Searl, Richard H. ..... Faribault

SECRETARY
Watts, George W. ..... Faribault

Bauer, Paul G. ..... Faribault
‡ Beaton, J. Gordon ..... Northfield
‡ Bruhl, Heinz H. ..... Faribault
Buesgens, Ralph H. ..... Waterville
† Clarke, Dean ..... Faribault
‡ Engberg, Edward J. ..... Faribault
Francis, David W. ..... Morristown
Good, Roy H. ..... Northfield
‡ Graham, Asa B. ..... Faribault
‡ Haas, Jack F. ..... Northfield
‡ Halvorson, David C. ..... Northfield
† Kennedy, George L. ..... Faribault
Kolars, James J. ..... Faribault
Lende, Norman ..... Faribault
Meyer, Frederick C. ..... Kenyon
Meyer, Paul F. ..... Faribault
Meyer, Richard H. ..... Faribault
Meyer, Robert P. ..... Faribault
‡ Neutzman, Arthur W. ..... Faribault
‡ Orr, Burton A. ..... Faribault
Rumpf, Carl W. ..... Faribault
Rysgaard, George N. ..... Northfield
‡ Searl, Richard H. ..... Faribault
‡ Smith, Thorsten ..... Faribault
‡ Speckals, Robert C. ..... Faribault
‡ Street, Bernard ..... Northfield
Studer, Donald J. ..... Faribault
† Traeger, Carl A. ..... Faribault
‡ Watts, George W. ..... Faribault
‡ Weaver, Paul H. ..... Faribault

ST. LOUIS COUNTY MEDICAL SOCIETY

Carlton, Cook, Lake and Southern portion of
St. Louis County
Regular meetings, second Thursday in each month
except July and August
Annual meeting, second Thursday in January
Number of members 203

PRESIDENT
Balmer, Albert I. ..... Duluth

SECRETARY
Reardon, Andrew E. ..... Duluth

SECRETARY, EXECUTIVE OFFICE
Lundgren, Miss Margaret M. ..... Duluth
‡ Anderson, James M. ..... Duluth
‡ Abraham, Arden L. ..... Duluth
‡ Ahrens, Curtis F. ..... Duluth
‡ Asta, Joseph J. ..... Duluth
† Athens, A. G. ..... Santa Barbara, CA
‡ Atmore, William G. ..... Duluth
‡ Aufderheide, Arthur C. ..... Duluth
‡ Backus, Byron C. ..... Cloquet
‡ Backus, Lloyd B. ..... Cloquet
‡ Backus, Reno W. ..... Nopeming
‡ Bagley, Charles M. ..... Duluth
Bagley, Elizabeth C. ..... Duluth
‡ Bakkila, Henry E. ..... Duluth
‡ Balmer, Albert I. ..... Duluth
‡ Bardon, Richard ..... Duluth
‡ Barker, John D. ..... Duluth
† Barney, Leon A. ..... Duluth
‡ Barrett, Earl E. ..... Duluth
‡ Bartzen, Peter J. ..... Duluth
‡ Becker, Frederic T. ..... Duluth
‡ Bell, Harry M., Jr. ..... Duluth
Bepko, Marie K. (Mrs. Puumala) ..... Cloquet
† Berdez, George L. ..... Duluth
‡ Bergan, Robert O. ..... Duluth
†‡ Bianco, Anthony J. ..... Vero Beach, FL
‡ Bloom, Joseph ..... Silver Bay
‡ Boecker, Bernhard ..... Duluth
Boman, Paul G. ..... Duluth
‡ Boyer, Samuel H. ..... Duluth
‡ Bray, Philip N. ..... Duluth
‡ Brooker, Warren J. ..... Duluth

Continued on Next Page

St. Louis County Medical Society *(Continued)*

‡ Brown, Cyrus C., Jr. ..... Duluth
‡ Buckley, Robert P. ..... Duluth
‡ Bulluck, Matthew H. ..... Duluth
‡ Butler, John K. ..... Cloquet

‡ Campaigne, Robert J. ..... Duluth
‡ Christensen, Clarence H. ..... Duluth
Church, Gerald E. ..... Two Harbors
Clark, Elizabeth A. (Mrs. Halbert) ..... Duluth
‡ Clark, Ivan T. ..... Duluth
‡ Coll, James J. ..... Duluth
† Collins, Arthur N. ..... Duluth
‡ Conley, Francis W. ..... Duluth
‡ Cottor, Robert E. ..... Duluth
‡ Coventry, William D. ..... Duluth
‡ Cowan, George M. ..... Duluth
‡ Creps, James R. ..... Duluth

Davis, William ..... Moose Lake
‡ Deutsch, Robert J. ..... Duluth
‡ Dickson, Franklin H. ..... Proctor
‡ Dietrich, Donald E. ..... Duluth
‡ Dobbs, Richard L. ..... Duluth
‡ Drexler, Charles J. ..... Duluth
‡ Dwyer, John J. ..... Duluth

‡ Eckman, Philip F. ..... Duluth
‡ Eckman, Philip L. ..... Duluth
‡ Eckman, Ralph J. ..... Duluth
‡ Eklund, Carl D. ..... Duluth
‡ Emanuel, Karl W. ..... Duluth
* Eppard, Raymond M. ..... Cloquet
Evison, Emerson O. ..... Duluth

‡ Fawcett, Keith R. ..... Duluth
‡ Fellows, Manley F. ..... Duluth
‡ Feuling, John C. ..... Duluth
‡ Fifield, Malcolm M. ..... Duluth
*†‡Fischer, Mario M. ..... Duluth
‡ Fisketti, Henry ..... Duluth
‡ Fuller, Josiah ..... Duluth

‡ Gillespie, Malcolm G. ..... Duluth
† Gobel, Fredarick L. ..... Minneapolis
‡ Goldish, Daniel R. ..... Duluth
‡ Goldish, Robert J. ..... Duluth
‡ Goldschmidt, Volker ..... Duluth
‡ Goodnow, William H. ..... Duluth
‡ Gowan, Lawrence R. ..... Duluth
‡ Gowan, Lawrence R., Jr. ..... Duluth
‡ Grohs, William H. ..... Duluth
‡ Gronquist, Y. K. J. ..... Cloquet

‡ Haavik, John E. ..... Duluth
Halbert, John J. ..... Duluth
‡ Halliday, Phillip V. ..... Duluth
Hanson, Ernest O. ..... Cloquet
‡ Harrington, Vernon A. ..... Duluth
‡ Heisel, John G. ..... Duluth
Henry, Harold W. ..... Moose Lake
‡ Hilding, Anderson C. ..... Duluth
† Hirschboeck, Frank J. ..... Duluth
‡ Hoeg, Dwight C. ..... Duluth
‡ Hoff, Herbert O. ..... Duluth
‡ Holt, Glen E. ..... Duluth
‡ Houglum, Arvid J. ..... Duluth
‡ Houkom, S. Sverre ..... Duluth
Hutchinson, Henry ..... St. Cloud

Jacklin, Alexander J. ..... Duluth
‡ Jacobson, Ferdinand C. ..... Duluth
‡ Jacott, William E. ..... Duluth
† Jensen, Thorvold J. ..... Duluth
‡ Jeronimus, Henry J. ..... Duluth
Jessico, Charles M. ..... Duluth
‡ Johnson, Franklin L. ..... Duluth
‡ Johnson, Karl E. ..... Duluth
#‡Johnson, Theodore L. ..... Duluth
‡ Juntunen, Roy R. ..... Duluth

Kilen, Mark ..... Ft. Lewis, WA
†‡ Klein, Harry ..... Duluth
*†‡Klein, William A. ..... Duluth
‡ Knoedler, John P. ..... Duluth
*† Kohlbry, Carl O. ..... Duluth
Kosiak, William ..... Two Harbors
‡ Krueger, Victor R. ..... Nopeming
‡ Kundel, Donald W. ..... Duluth

‡ L'Abbe, A. J. Philip ..... Duluth
‡ LaBree, Robert H. ..... Duluth
Langseth, Rodney N. ..... Ft. Leavenworth, KS
‡ Larson, Donald M. ..... Duluth
Larson, Keith D. ..... Moose Lake
Larson, Kenneth R. ..... Moose Lake
‡ Latterell, Kenneth E. ..... Duluth
‡ Leek, Joseph H. ..... Duluth
† Lepak, Francis J. ..... Duluth
Leppink, Harold B. ..... Two Harbors
Leppo, N. Erkki A. ..... Duluth
Linke, Charles A. ..... Duluth
Linke, Clara L. ..... Duluth
†‡ Litman, Samuel N. ..... Duluth

†‡ McNutt, John R. ..... Duluth
MacDonald, Roger A. ..... Grand Marais
‡ MacRae, Gordon C. ..... Duluth
† Magney, Fredolph H. ..... Duluth
Martin, Webster C. ..... Duluth
‡ Maryland, Daniel L. ..... Duluth
† Mayne, Roy M. ..... St. Paul
‡ Mendesh, Anthony N. ..... Duluth
‡ Merrick, William G. ..... Duluth
‡ Meyer, Howard J. ..... Duluth
Michaelis, Dorothy ..... Duluth
† Moe, Thomas ..... Moose Lake
Moller, Julie C. ..... Duluth
Monge', James J. ..... Duluth
‡ Monserud, Nels O. ..... Cloquet
‡ Moyer, John B. ..... Duluth
‡ Munger, James E. ..... Duluth
Munson, Martin S. ..... Moose Lake

‡ Nisius, George F. ..... Duluth
‡ Nisswandt, Albert L. ..... Duluth
†‡ Norberg, Carl E. ..... Los Altos, CA

‡ O'Neill, John C. ..... Duluth

‡ Parson, E. Irvine ..... Duluth
‡ Pasek, Antone W. ..... Cloquet
Patch, Orien B. ..... Duluth
‡ Pedersen, Roy C. ..... Duluth
‡ Peterson, John H. ..... Duluth
Pollard, William S. ..... Duluth
‡ Power, John E. ..... Duluth
Puumala, Barbara M. ..... Cloquet
Puumala, Reino H. ..... Cloquet
Puumala, Ricard R. ..... Cloquet

‡ Reardon, Andrew E. ..... Duluth
‡ Reed, Henry H. ..... Duluth
Rosenquist, Rudolph J. ..... Glencoe
Rowe, Richard G. ..... Silver Bay
‡ Rudie, Peter S. ..... Duluth
‡ Rudie, William D. ..... Duluth

St. Louis County Medical Society *(Continued)*

‡ Runquist, John M. ..... Duluth
‡ Ruth, Bradley R. ..... Duluth
‡ Ryan, Edward A. ..... Duluth
Sach-Rowitz, Alvan ..... Moose Lake
Saloum, Lucille M. ..... Duluth
Sanford, John B. ..... Duluth
Sax, Milton H. ..... Duluth
Sax, Simon G. ..... Duluth
‡ Schmid, John F. ..... Duluth
‡ Schneider, Lawrence E. ..... Duluth
Sherman, Roger W. ..... Miami, FL
‡ Shirley, Raymond M. ..... Duluth
Slack, William J. ..... Duluth
‡ Smith, Cyril M. ..... Duluth
Smith, Wallace R. ..... Grand Marais
Spang, Anthony ..... Duluth
‡ Spang, James S. ..... Duluth
‡ Spang, William M. ..... Duluth
‡ Stein, William A. ..... Duluth
‡ Storsteen, Kenneth A. ..... Duluth
‡ Streitz, John M. ..... Duluth
‡ Strewler, Gordon J. ..... Duluth
‡ Swedberg, William A. ..... Duluth
‡ Swensen, Don P. ..... Duluth
‡ Swenson, Arnold O. ..... Duluth
Teich, Kenneth W. ..... Pontiac, MI
‡ Terrell, Bernard J. ..... Nopeming
‡ Tetlie, James P. ..... Duluth
‡ Thomas, John V. ..... Duluth
Thompson, James I. ..... Duluth
‡ Thurn, Roy J. ..... Duluth
‡ Tosseland, Noel E. ..... Duluth
‡ Ulrich, Emery E. ..... Duluth
Van Druten, William A. ..... Duluth
‡ Van Druten, William A. ..... Duluth
Van Ryzin, Donald J. ..... Duluth
‡ Walder, Harold J. ..... Duluth
‡ Wall, Jack E. ..... Duluth
‡ Wallace, Martin O. ..... Duluth
‡ Wells, Arthur H. ..... Duluth
‡ Williams, Bruce F. P. ..... Duluth
‡ Wolfe, John W. ..... Duluth
‡ Young, Hadley R. ..... Duluth
*††Young, Thomas O. ..... Duluth

SCOTT-CARVER COUNTY MEDICAL SOCIETY

Scott and Carver Counties
Regular meetings, first Tuesday of each month,
except July and August
Annual meeting in June
Number of members 39

PRESIDENT

Adams, Patrick J. ..... Shakopee

SECRETARY

Lukk, Olaf ..... Prior Lake
‡ Adams, Patrick J. ..... Shakopee
Bean, Charles N. ..... Waconia
‡ Bratholdt, James W. ..... Watertown
† Buck, Frederick H. ..... Shakopee
‡ Cervenka, Charles F. ..... New Prague
Clarke, John W. ..... Waconia
‡ Doherty, Elmer M. ..... New Prague
‡ Erickson, Robert L. ..... Rosemount
‡ Gildersleeve, Robert G. ..... Watertown
‡ Hallgren, Roger B. ..... Belle Plaine
† Hebeinsen, Milton B. ..... Chaska
Heinz, Ivy ..... Shakopee
‡ Heinzerling, Carl R. ..... Chaska
††‡ Juergens, Herman M. ..... Belle Plaine
† Kucera, Stanley T. ..... Northfield
‡ Kuz, Eugene ..... Savage
Larson, Leighton W. ..... Waconia
‡ Lehrer, Alfred J., Jr. ..... Montgomery
‡ Lukk, Olaf ..... Prior Lake
† McDaniel, Samuel P. ..... Lakeville
‡ Mendiola, Ramon P., Jr. ..... Waconia
Moller, Jurgen ..... St. Paul
‡ Nelson, Gerald E. ..... Chaska
‡ Olson, Richard E. ..... Chaska
‡ Pearson, Bror F. ..... Shakopee
‡ Philp, David R. ..... Watertown
‡ Pistulka, Rolland D. ..... Chaska
‡ Ponterio, James E. ..... Shakopee
Provence, Cecil L. ..... Waconia
Rieschl, Elizabeth K. ..... Jordan
Rynda, Edwin ..... New Prague
Savaryn, John P. ..... Waconia
‡ Schimelpfenig, George T. ..... Chaska
‡ Smith, David G. ..... Watertown
‡ Spagnolo, Anthony A. ..... Shakopee
Stahler, Paul A. ..... Jordan
‡ Tuma, Ben ..... Faribault
‡ Wempner, Jon D. ..... Waconia
††‡ Westerman, Alvin E. ..... Montgomery
††‡ Westerman, Fred C. ..... Montgomery

SIBLEY COUNTY MEDICAL SOCIETY

Sibley County
Regular meetings, 3rd Monday of Odd number months
Annual meeting in November
Number of members 6

PRESIDENT

Schroeppel, John E. ..... Winthrop

SECRETARY

Knoche, Harvey A. ..... Gaylord
‡ Dysterheft, Adolf ..... Gaylord
††‡ Greene, Gordon ..... Cherokee, IA
Kath, Reinhard H. ..... Arlington
Knoche, Harvey A. ..... Gaylord
‡ Schroeppel, John E. ..... Winthrop
Vener, John M. ..... Arlington

SOUTHWESTERN MINNESOTA MEDICAL SOCIETY

Cottonwood, Jackson, Murray, Nobles, Pipestone and Rock Counties
Regular meetings first Monday of each month except July and August
Annual meeting, November
Number of members 59

PRESIDENT

Plucker, Milton W. ..... Worthington

SECRETARY

Heiberg, O. M. ..... Worthington
‡ Bader, Jean L. ..... Slayton
‡ Basinger, Harold P. ..... Windom
†‡ Basinger, Homer P. ..... Windom
‡ Beckering, Gerrit ..... Edgerton
‡ Beckering, Roland G. ..... Edgerton
‡ Benjamin, Walter G. ..... Pipestone
‡ Berner, Herbert W., Jr. ..... Worthington
‡ Bofenkamp, Ferdinand W. ..... Luverne
‡ Boone, Ervin S. ..... Luverne
‡ Boyd, Frank E. ..... Pipestone
‡ Carlson, John V. ..... Westbrook
‡ Carlson, Lloyd E. ..... Worthington
‡ Christiansen, Harold A. ..... Jackson
‡ Dahlquist, La Rue ..... Pipestone
†‡ Daumann, Roy E. ..... Minneapolis
‡ Dawson, Lorin D. ..... Worthington
‡ Desai, B. J. ..... Worthington
‡ Dokken, James H. ..... Windom
‡ Doman, Victor W. ..... Lakefield
‡ Eaton, David B. ..... Worthington
‡ Faul, Bennie C. ..... Worthington
‡ Fitch, Charles G. ..... Worthington
‡ Glick, Dallas D. ..... Mountain Lake
†‡ Halloran, Walter H. ..... Jackson
‡ Halpern, David J. ..... Brewster
‡ Harrison, Percy W. ..... Worthington
‡ Hegstad, Thomas C. ..... Windom
‡ Heiberg, O. M. ..... Worthington
‡ Hoyer, Ludolf J. ..... Windom
‡ Johnson, Alan R. ..... Windom
‡ Keyes, Robert W. ..... Pipestone
‡ Kilbride, Edwin A. ..... Worthington
‡ Kotval, Russell J. ..... Pipestone
‡ Laikola, Leslie A. ..... Adrian
‡ Larsen, Russell H. ..... Lakefield
‡ Lohmann, John G. ..... Pipestone
*‡ McNear, George R., Jr. ..... Heron Lake
‡ Maitland, Edwin T. ..... Jackson
‡ Martin, Albert ..... Luverne
‡ Minge, Raymond K. ..... Worthington
‡ Nealy, Donald E. ..... Adrian
‡ Nywall, Dean D. ..... Slayton
‡ Odland, Donald M. ..... Luverne
‡ Patterson, Hugh D. ..... Slayton
‡ Pierce, Robert B. ..... Heron Lake
‡ Pierson, Roy F. ..... Slayton
†‡ Piper, William A. ..... Mountain Lake
‡ Plucker, Milton W. ..... Worthington
‡ Rud, Paul D. ..... Luverne
‡ Ryding, Vincent ..... Ames, IA
† Schade, Frederick ..... Santa Cruz, CA
‡ Seisler, Edward P. ..... Worthington
†‡ Sherman, Charles L. ..... Luverne
‡ Siebert, Darrel W. ..... Luverne
‡ Stam, John ..... Worthington
‡ Strand, Jack W. ..... Jasper
†‡ Stratte, Harold C. ..... Windom
‡ Wells, Walter B. ..... Jackson
‡ Wiens, Alvin L. ..... Mountain Lake
† Williams, Charles A. ..... Seattle, WA

STEARNS-BENTON COUNTY MEDICAL SOCIETY

Stearns and Benton Counties
Regular meetings, third Thursday of each month
Annual meeting, December
Number of members 89

PRESIDENT

Rozycki, Anthony ..... St. Cloud

SECRETARY

Sommers, Stephen D. ..... St. Cloud

SECRETARY, EXECUTIVE OFFICE

Kline, Mrs. Richard F. ..... St. Cloud
Alden, Charles W. ..... Sauk Rapids
Asp, Donald S. ..... Milaca
Aulick, Ernest J. ..... Paynesville
Autrey, William A. ..... St. Cloud
Ballantine, Jerome J. ..... St. Cloud
‡ Bancroft, Burton R., Jr. ..... St. Cloud
Barnett, Arthur ..... Foley
Bauman, John C. ..... Foley
Baumgartner, Florian H. ..... Albany
‡ Belshe, Joseph ..... St. Cloud
‡ Berger, Phil R. ..... St. Cloud
‡ Beuning, John B. ..... St. Cloud
‡ Bozanich, Milosh S. ..... St. Cloud
‡ Brattensborg, Henry J. ..... St. Cloud
‡ Brigham, Charles F., Jr. ..... St. Cloud
‡ Broker, Henry M. ..... St. Cloud
Brown, Frank T. ..... St. Cloud
‡ Cesnik, Robert J. ..... Sauk Rapids
†‡ Clark, Harry B. ..... St. Cloud
Cleaves, Wm. D. ..... Sauk Centre
‡ Cumming, Robert J. ..... St. Cloud
‡ Donaldson, Charles S. ..... St. Cloud
Dubois, Julian F. ..... Sauk Centre
Dzuibinski, Emil H. ..... St. Cloud
Espelien, Alan D. ..... St. Cloud
‡ Evans, Leslie M. ..... Sauk Rapids
‡ Gaida, Joseph B. ..... St. Cloud
‡ Gerstenkorn, George B. ..... Milaca
Goehrs, Gilman H. ..... St. Cloud
Grant, John C. ..... Sauk Centre
Halenbeck, Philip L. ..... St. Cloud
Harbaugh, John T. ..... St. Cloud
‡ Hedenstrom, Paul H. ..... Princeton

Stearns—Benton County Medical Society *(Continued)*

Held, Wm. J. ..... St. Cloud
† Henry, Clarence J. ..... Onamia
Henry, Joseph E. ..... Milaca
‡ Higdon, Donald A. ..... St. Cloud
‡ Hughes, Bernard J. ..... St. Cloud
‡ Jaeger, Dwight E. ..... St. Cloud
‡ John, Byron L. ..... St. Cloud
‡ Johnson, William E. ..... St. Cloud
†‡ Jones, Richard N. ..... St. Cloud
‡ Keith, Paul J. ..... Milaca
‡ Kelly, James H. ..... St. Cloud
‡ Kelly, John F. ..... Cold Spring
‡ Koenig, Robert P. ..... St. Cloud
‡ Koop, Severin H., Jr. ..... St. Cloud
‡ Kruzich, Stephen J. ..... St. Cloud
Kuhlmann, Lawrence B. ..... Melrose
Kvistberg, Gerald K. ..... St. Cloud
‡ LaFond, Edward M. ..... St. Cloud
Lenarz, Albert J. ..... St. Cloud
Lindemann, Raymond J. ..... Paynesville
‡ Lindley, Stanley B. ..... St. Cloud
‡ Loeb, George L. ..... St. Cloud
‡ Loes, Louis A. ..... St. Cloud
Luby, Thomas H. ..... St. Cloud
†‡ McDowell, John P. ..... St. Cloud
McNamara, John P. ..... Rice
‡ May, Robert B. ..... St. Cloud
‡ Moran, Paul T. ..... St. Cloud
Mueller, Rudolph B. ..... Richmond
‡ Murn, Thomas G. ..... St. Cloud
‡ Murray, Robert A., Jr. ..... St. Cloud
Musachio, Nicholas F. ..... St. Paul
Myre, Clifford R. ..... Paynesville
Neils, Vernon E. ..... St. Cloud
Nietfield, Aloys B. ..... Sauk Centre
‡ O'Keefe, James P. ..... St. Cloud
‡ Olinger, John N. ..... St. Cloud
‡ Petersen, Robert T. ..... St. Cloud
‡ Phares, Otto C. ..... St. Cloud
‡ Raetz, Sylvester J. ..... Maple Lake
‡ Richards, William B. ..... St. Cloud
Ritchie, Donald A. ..... St. Cloud
‡ Rozycki, Anthony T. ..... St. Cloud
Salk, Richard J. ..... Albany
Savelkoul, Gene R. ..... Belgrade
Schamber, Walter ..... St. Cloud
‡ Schmitz, Everett J. ..... St. Cloud
Sisk, Harvey E. ..... St. Cloud
Slanga, Roger A. ..... St. Cloud
‡ Smith, J. Weston ..... St. Cloud
Stahn, Louis H. ..... St. Cloud
‡ Sommers, Stephen D. ..... St. Cloud
Stiles, Clifford D. ..... Foley
Thienes, R. Lawrence ..... St. Cloud
Vanderpool, Thomas E. ..... Paynesville
‡ Veranth, Leonard A. ..... St. Cloud
‡ Wenner, Waldemar T. ..... St. Cloud
‡ Wittrock, Louis H. ..... Watkins
Zachman, Albert H. ..... Melrose
‡ Zeleny, Joseph H. ..... St. Cloud

STEELE COUNTY MEDICAL SOCIETY

Steele County
Regular meetings, third Tuesday of every other month
Annual meeting, November
Number of members 25

PRESIDENT
Henry, John C. ..... Owatonna
SECRETARY
Arnesen, John F. ..... Owatonna
‡ Anderson, Franklin C. ..... Owatonna
Arnesen, John F. ..... Owatonna
Buresh, Kenneth L. ..... Owatonna
‡ deWerd, Robert W. ..... Owatonna
Dewey, Donald H. ..... Owatonna
† Fischer, John R. ..... Parkway, MO
‡ Floersch, Adrian J. ..... Owatonna
‡ Halvorsen, Daniel K. ..... Owatonna
Hartung, Elmer H. ..... Claremont
‡ Henry, John C. ..... Owatonna
‡ Henry, Kenneth G. ..... Owatonna
‡ Hilker, Robert T. ..... Owatonna
Honath, Donald H. ..... Owatonna
Kulstad, Oscar S. ..... Dodge Center
Linnell, Leonard S. ..... Owatonna
Lundquist, Curt W. ..... Owatonna
McEnaney, James E. ..... Owatonna
† McIntyre, John A. ..... Owatonna
† Morehead, Dewey E. ..... Bodega Bay, CA
Nealy, Timothy E. ..... Blooming Prairie
‡ Olson, Albert J. ..... Owatonna
Roberts, Oliver W. ..... Owatonna
Schaefer, Joseph F. ..... Owatonna
Stransky, Theodore W. ..... Owatonna
† Wilkowske, Rudolph J. ..... Owatonna

UPPER MISSISSIPPI MEDICAL SOCIETY

Aitkin, Cass, Crow Wing, Hubbard, Morrison, Todd & Wadena Counties
Regular meetings, January, May, September
Annual meeting, January
Number of members 76

PRESIDENT
Seifert, Donald R. ..... Little Falls
SECRETARY
Anderson, Arden O. ..... Brainerd
‡ Aga, John H. ..... Brainerd
‡ Anderson, Arden O. ..... Brainerd
† Anderson, Werner W. ..... Cincinnati, OH
†‡ Badeaux, George I. ..... Brainerd
Belcher, Royden A. ..... Little Falls
‡ Bender, James H. ..... Brainerd
* Benson, A. H. ..... Little Falls
‡ Bissinger, Lester L. ..... Brainerd
Bolstad, Owen C. ..... Reno, NV
‡ Borgerson, Arthur H. ..... Long Prairie
‡ Brown, Russell T. ..... Browerville

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Upper Mississippi Medical Society *(Continued)*

Burman, Richard E. ..... Aitkin
‡ Cardle, George E. ..... Brainerd
Closuit, Frederick C. ..... Aitkin
‡ Coombs, Carl H. ..... Cass Lake
Crow, Earl R. ..... Minnetonka
† Davis, Lloyd T. ..... Wadena
Davis, Luther F. ..... Wadena
‡ Dodson, Albertus F. ..... Brainerd
‡ Erickson, Alvin O. ..... Long Prairie
‡ Fitzsimons, William E. ..... Brainerd
Fortier, George M. A. ..... Little Falls
Fuglestad, J. Roald ..... Brainerd
Gamm, Edgar R. ..... Park Rapids
† Ghostley, Mary C. ..... Minneapolis
Grimes, Paul T. ..... Park Rapids
‡ Grose, Frederick N. ..... Clarissa
Halme, William B. ..... Wadena
Hansen, Milo L. ..... Little Falls
Haugen, Norman R. ..... Park Rapids
Heid, James K. ..... Little Falls
‡ Johnson, Douglas L. ..... Little Falls
‡ Kanne, Earl R. ..... Brainerd
‡ Kelley, Roger E. ..... Crosby
Knipp, William J. ..... Brainerd
‡ Knoll, W. V. ..... Brainerd
Larson, Theodore G. ..... Brainerd
‡ Lee, Hubert W. ..... Brainerd
Lelwica, Thaddeus J. ..... Staples
Lofstrom, Dennis E. ..... Brainerd
Longfellow, Helen W. ..... Brainerd
Lund, Werner J. ..... Staples
‡ McLane, William O. ..... Brainerd
‡ Marshall, Clark M. ..... Crosby
‡ Marvin, Joseph E. ..... Brainerd
‡ Meller, Maurice ..... Brainerd
Mortenson, Howard O. ..... Menahga
‡ Mosby, Maurice E. ..... Long Prairie
‡ Mulligan, Arthur M. ..... Brainerd
Ness, Duane E. ..... Wadena
‡ Nixon, James B. ..... Crosby
‡ O'Leary, John B. ..... Brainerd
Olson, Lillian A. ..... Ah-Gwah-Ching
Parker, Charles W. ..... Wadena
Parker, Warren E. ..... Sebeka
‡ Pedersen, Robert L. ..... Brainerd
‡ Pelzl, Charles R. ..... Pine River
Petraborg, Harvey T. ..... Aitkin
Pettersen, George R. ..... Aitkin
‡ Poppie, Robert W. ..... Brainerd
‡ Reichelderfer, Charles F. ..... Staples
‡ Reichelt, Leland G. ..... Wadena
Rhodes, Clinton E. ..... Park Rapids
‡ Ringle, Otto F. ..... Walker
Scanlon, Hugh A. ..... Little Falls
† Schrantz, Robert D. ..... Phoenix, AZ
† Schulberg, Verne A. ..... Minneapolis
Seifert, Donald R. ..... Little Falls
Spieler, F. B. ..... Pequot Lakes
‡ Stein, Raymond J. ..... Pierz
Stoy, Robert A. ..... Little Falls
Vandersluis, Charles W. ..... Minneota
Watson, Sidney W. ..... Little Falls
‡ Westley, Kent F. ..... Little Falls
Wiger, Oliver E. ..... Little Falls
† Will, William W. ..... Erskine
‡ Williams, Mervyn M. ..... Ah-Gwah-Ching
Witter, Robert L. ..... Wadena

WABASHA COUNTY MEDICAL SOCIETY

Wabasha County
Regular meetings, special call
Annual meeting first Thursday after first Monday in October
Number of members 13

PRESIDENT

Bouquet, Bertram J. ..... Wabasha

SECRETARY

Gjerde, William P. ..... Lake City
‡ Bayley, E. Covell ..... Lake City
‡ Bouquet, Bertram J. ..... Wabasha
‡ Bowers, Robert N. ..... Lake City
‡ Ellis, Earl W. ..... Elgin
‡ Gjerde, William P. ..... Lake City
† Habein, Harold C. ..... Palo Alto, CA
‡ Mahle, Donald G. ..... Wabasha
‡ Martin, David E., III ..... Wabasha
Martin, Doreen A. ..... Pepin, Wis.
Nehring, John ..... Wabasha
† Ochsner, Clarence G. ..... Santa Barbara, CA
† Replogle, William H. ..... Los Angeles, CA
‡ Sontag, David W. ..... Lake City

WASECA COUNTY MEDICAL SOCIETY

Waseca County
Regular meetings, Bimonthly
Annual meeting, January
Number of members 8

PRESIDENT

Oeljen, S. C. G. ..... Waseca

SECRETARY

Normann, Stephen T. ..... Waseca
Davis, Raymond D. ..... Stockton, CA
‡ Hottinger, Raymond C. ..... Janesville
‡ Johnson, Curtis A. ..... Olivia
‡ Normann, Stephen T. ..... Waseca
‡ Oeljen, S. C. G. ..... Waseca
‡ Olds, George H. ..... New Richland
‡ Rohrer, Thomas P. ..... Waseca
‡ Swenson, Orvie J. ..... Waseca

WASHINGTON COUNTY MEDICAL SOCIETY

Washington and Dakota Counties
Regular meetings, first Tuesday in each month
Annual meeting, June
Number of members 28

PRESIDENT
Weiss, Carl A. ..... Hastings
SECRETARY
Peterson, John O. H. ..... Hastings
‡ Bealka, Neil ..... Stillwater
† Brabec, Paul F. ..... Hastings
‡ Carlson, Russel E. ..... Stillwater
Cowger, Robert C. ..... Farmington
Dale, Les N. ..... Hastings
† Eiden, Vera M. ..... Afton
Fasbender, Herman T. ..... Hastings
Foderick, John W. ..... Hastings
Hegrenes, Robert L. ..... Farmington
† Holcomb, Joel T. ..... Marine-on-St. Croix
Hunter, Murray H. ..... Farmington
‡ Jenson, James E. ..... Stillwater
Johnson, O. Guy ..... Bayport
‡ Johnson, Robert H. ..... Bayport
Juergens, Manley F. ..... Stillwater
Karabeyoglu, A. Turgut ..... Hastings
‡ Kiolbasa, Edward B. ..... Stillwater
Kulzer, Norbert J. ..... Hastings
‡ McCarten, Francis M. ..... Stillwater
‡ Murphy, Thomas R. ..... Stillwater
Peterson, John O. H. ..... Hastings
† Poirier, Joseph A. ..... White Bear Lake
Ruggles, George M. ..... Forest Lake
†‡ Sherman, Carnot H. ..... Bayport
‡ Stratte, Jon R. ..... Stillwater
†‡ Stuhr, John W. ..... Stillwater
Weiss, Carl A. ..... Hastings
Zeller, Hector ..... Hastings

WEST CENTRAL MINNESOTA MEDICAL SOCIETY

Big Stone, Pope, Stevens and Traverse Counties
Regular meetings, second Tuesday in March, May, September and November
Annual meeting, November
Number of members 22

PRESIDENT
Winge, H. C. ..... Wheaton
SECRETARY
Kolp, Berton A. ..... Glenwood
‡ Arneson, Arthur I. ..... Morris
Benjamin, Charles I. ..... Glenwood
† Bergan, Otto ..... Clinton
‡ Brace, Ray I. ..... Clinton
‡ Bucher, Foster D. ..... Starbuck
‡ Christenson, Carl E. ..... Clinton
‡ Eide, O. A. ..... Hancock
‡ Hedemark, Homer H. ..... Ortonville
Hedemark, Truman A. ..... Ortonville
Knip, Robert J. ..... Ortonville
‡ Kolp, Berton A. ..... Glenwood
‡ Kooda, Jennings C. ..... Morris
‡ Kozel, William J. ..... Morris
‡ Lee, Gordon E. ..... Glenwood
‡ Magnuson, Allen E. ..... Wheaton
Merrill, Robert ..... Des Moines, IA
‡ Popoff, Russel G. ..... Graceville
‡ Rossberg, Raymond A. ..... Morris
‡ Winge, H. C. ..... Wheaton
‡ Zempel, Alan R. ..... Starbuck

WINONA COUNTY MEDICAL SOCIETY

Winona County
Regular meetings, second Monday in January, April, July and October
Annual meeting, January
Number of members 33

PRESIDENT
Degallier, Daniel ..... Winona
SECRETARY
Heise, Herbert vR. ..... Winona
‡ Boardman, Dalmon V. ..... Winona
‡ Christensen, Eli E. ..... Winona
‡ Degallier, Daniel ..... Winona
‡ Fenske, Arnold ..... Winona
‡ Finkelnburg, William ..... Winona
‡ Garber, George L. ..... Winona
‡ Haesly, Warren W. ..... Winona
‡ Hartwich, Roger F. ..... Winona
‡ Hawk, Dale J. ..... St. Charles
‡ Heise, Carl vR. ..... Winona
‡ Heise, Herbert vR. ..... Winona
‡ Heise, Paul vR. ..... Winona
‡ Heise, Philip vR. ..... Winona
‡ Heise, William vR. ..... Winona
‡ Hughes, Sidney O. ..... Winona
‡ Johnson, Curtis M. ..... Winona
‡ Johnston, Leonard ..... Winona
*†‡Keyes, John D. ..... Winona
‡ Loomis, George L. ..... Winona
†‡ McLaughlin, Edmund M. ..... Winona
Mattison, Percy A. ..... Winona
† Meinert, Albert E. ..... Winona
‡ Peterson, John R. ..... Rushford

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Winona County Medical Society *(Continued)*

‡ Roemer, Henry J. ..... Winona
‡ Rogers, Charles W. ..... Winona
Schafer, Charles F. ..... Winona
† Schmidt, Hilmer R. ..... Rushford
‡ Testor, James V. ..... Winona
‡ Tweedy, John A. ..... Winona
‡ Tweedy, Robert B. ..... Winona
Vollmer, Frederick J. ..... Winona
‡ Wilson, L. J. ..... Rushford
†‡ Wilson, R. H. ..... Lamoille
‡ Younger, Lewis I. ..... Winona

WRIGHT COUNTY MEDICAL SOCIETY

Wright County
Regular meetings, first Tuesday of every other month
Annual meeting in November
Number of members 16

PRESIDENT
Sandeen, Robert M. ..... Buffalo
SECRETARY
Maus, Donald J. ..... Monticello
‡ Anderson, Waldo P. ..... Buffalo
‡ Bendix, Lester H. ..... Annandale
‡ Catlin, Theodore J. ..... Buffalo
†‡ Ellison, Frank E. ..... Monticello
‡ Greenfield, W. Theodore ..... Cokato
‡ Guilfoile, Pierre J. ..... Delano
‡ Hart, William E. ..... Monticello
‡ Maus, Donald J. ..... Monticello
‡ Purves, G. Harland ..... Buffalo
‡ Sandeen, Robert M. ..... Buffalo
Shin, Rok ..... Howard Lake
‡ Smorstok, Matthew B. ..... Monticello
‡ Steiner, Andrew M. ..... St. Michael
†‡ Thielen, R. D. ..... New Brighton
‡ Whitesell, L. A., Jr. ..... Buffalo
Zapf, John D. ..... Monticello

ZUMBRO VALLEY MEDICAL SOCIETY

Olmsted, Houston, Fillmore and Dodge Counties
Regular meetings, first Wednesday of every odd-numbered month
Annual meeting, first Wednesday of November
Number of members 626

PRESIDENT
Utz, David C. ..... Rochester
SECRETARY
Spencer, Robert J. ..... Rochester
EXECUTIVE SECRETARY
Fricke, Robert E. ..... Rochester
‡ Aaro, Leonard A. ..... Rochester
‡ Adson, Martin A. ..... Rochester
‡ Affeldt, Daniel E. ..... Kasson
† Ahlfs, Jacob J. ..... Ft. Lauderdale, FL
Ahmann, David L. ..... Rochester
#† Aldrete, Joaquin S. ..... San Antonio, TX
Allen, Raymond A. ..... Rochester
Allocco, Dominic J. ..... San Francisco, CA
† Altman, Robert L. ..... Rochester
† Amberg, Samuel ..... Rochester
‡ Andersen, Howard A. ..... Rochester
†‡ Anderson, Mark J. ..... Sun City, AZ
‡ Anderson, Markham J., Jr. ..... Rochester
‡ Anderson, Milton W. ..... Rochester
† Arkin, Charles R. ..... Rochester
† Armbruster, Robert M. ..... Rochester
Arnold, Gordon B. ..... Cupertino, CA
† Ashby, Thomas M. ..... Rochester
Auerbach, Arthur M. ..... Hartford, CT
‡ Baggenstoss, Archie H. ..... Rochester
Bahn, Robert C. ..... Rochester
‡ Bair, Hugo L. ..... Rochester
‡ Baird, Raymond L. ..... Harmony
¶ Bajec, Dusan ..... Belgrade, Yugoslavia
‡ Baker, George S. ..... Rochester
† Baker, Harry R. ..... Hayfield
‡ Baker, Hillier L., Jr. ..... Rochester
Baker, James A. ..... Ft. Campbell, KY
Balfour, William M. ..... Lawrence, KS
Banfield, Frederick D. ..... Rochester
‡ Banner, Edward A. ..... Rochester
† Barbee, Charles W., Jr. ..... Rochester
†‡ Barker, Nelson W. ..... Rochester
† Barnes, Arlie R. ..... Rochester
‡ Barry, Maurice J., Jr. ..... Rochester
‡ Bartholomew, Lloyd G. ..... Rochester
‡ Bastron, James A. ..... Rochester
† Baumgartner, Carl J., Jr. ..... Rochester
Bayrd, Edwin D. ..... Rochester
‡ Beabout, John W. ..... Rochester
‡ Beahrs, Oliver H. ..... Rochester
† Beachamps, Gerald J. ..... Rochester
† Beckenbaugh, Robert D. ..... Rochester
† Beckering, Raymond E. ..... Rochester
‡ Belau, Paul G. ..... Rochester
† Bell, Richard A. ..... Rochester
† Benedict, William L. ..... Rochester
‡ Bennett, Clayton J. ..... Rochester
‡ Berge, Kenneth G. ..... Rochester
† Bergh, Allen V. ..... Rochester
†‡ Berkman, John M. ..... Rochester
‡ Bernatz, Philip E. ..... Rochester
‡ Bianco, Anthony J., Jr. ..... Rochester
‡ Bickel, William H. ..... Rochester
Bickford, Joyce A. ..... Rochester
† Bieger, R. Cyril ..... Rochester
† Bigelow, Charles E. ..... Dodge Center
† Bilstad, James M. ..... Rochester
‡ Bisel, Harry F. ..... Rochester
‡ Black, B. Marden ..... Rochester
† Blondin, Claude ..... Rochester

Zumbro Valley Medical Society *(Continued)*

† Blossman, Robert C. ..... Rochester
† Boman, Peter L. ..... Rochester
† Bonebrake, Robert A. ..... Rochester
† Bosland, Jon H. ..... Rochester
Botting, Arthur J. .....APO San Francisco, CA
† Bower, Philip J. ..... Rochester
† Bowers, Frank R. ..... Rochester
‡ Bowie, E. J. Walter ..... Rochester
† Boyd, Allen S., Jr. ..... Rochester
‡ Boyd, David A., Jr. ..... Rochester
† Boyer, Stanley W. ..... Rochester
† Braasch, William F. ..... Rochester
† Brand, Frank R. .....Columbia, MO
‡ Brandenburg, Robert O. ..... Rochester
† Brinkman, James F. ..... Rochester
‡ Broadbent, James C. ..... Rochester
‡ Brodhun, John C. ..... Rochester
† Brookler, Kenneth H. ..... Rochester
†‡ Brown, Alex E. ..... Bradenton, Fl.
‡ Brown, Arnold L. ..... Rochester
Brown, Donald I. .....Ventnor, NJ
‡ Brown, Henry A. ..... Rochester
‡ Brown, Joe R. ..... Rochester
† Brown, Patrick M. ..... Rochester
†‡ Brown, Philip W. ..... Rochester
‡ Brown, Philip W., Jr. ..... Rochester
Bryar, George E. ..... San Francisco, CA
† Bucchiere, John J., Jr. ..... Rochester
† Buie, Louis A. ..... Rochester
‡ Burbank, Mahlon K. ..... Rochester
† Burge, Kelmar M., Jr. ..... Rochester
‡ Burgert, E. O., Jr. ..... Rochester
‡ Burich, Harry F. ..... Rochester
‡ Burke, Edmund C. ..... Rochester
‡ Burton, Robert C. ..... Rochester
Buscemi, Michael F. ..... Belleville, N. J.
† Bush, Stephen T. ..... Rochester
‡ Butt, Hugh R. ..... Rochester
† Byron, Robert S. ..... Rochester

‡ Cain, James C. ..... Rochester
† Caldwell, Joseph G. ..... Rochester
† Cali, Robert W. ..... Rochester
‡ Callahan, John A. ..... Rochester
‡ Campbell, Donald C. ..... Rochester
‡ Campbell, Malcolm K. ..... Rochester
‡ Carlson, Harley C. ..... Rochester
Carney, Francoise ..... Rochester
Carr, David T. ..... Rochester
† Carrington, Stewart G. ..... Rochester
‡ Carryer, Haddon M. ..... Rochester
‡ Carter, Earl T. ..... Rochester
Cecil, James W. ..... Marysville, CA
Cerino, Lawrence E. ..... Pompano Beach, FL
‡ Childs, Donald S., Jr. ..... Rochester
† Chiroff, Richard T. ..... Rochester
Chung, Stanley M. K. .....Biloxi, MS
‡ Christensen, Norman A. ..... Rochester
‡ Clagett, O. Theron ..... Rochester
† Clark, Edward C. .....San Francisco, CA
† Clark, Leslie W. ..... Manchester, IA
† Clifton, Theodore A. .....Hollywood, FL
Code, Charles F. ..... Rochester
Coder, Donald M. .....Portsmouth, VA
‡ Cody, D. Thane ..... Rochester
† Cohen, Manley ..... Rochester
‡ Colby, Malcolm Y., Jr. ..... Rochester
† Coleman, Robert L. ..... Rochester
Coles, Douglas T. ..... Rochester
† Collins, Roger T. ..... Rochester
† Collison, Robert W. ..... Rochester
‡ Connolly, Daniel C. ..... Rochester
‡ Cook, Edward N. ..... Rochester
Cooper, Herbert A. ..... Wheatland, CA
‡ Cooper, Talbert ..... Rochester
‡ Corbin, Kendall B. ..... Rochester
Corcoran, James R. .....FPO New York, NY
Corrigan, Cyril J. ..... Rochester
† Cotton, Gerald ..... Rochester
‡ Coventry, Markham B. ..... Rochester
† Creasman, John P. ..... Rochester
† Crowder, Bennett L., II .....Ft. Campbell, KY
† Culligan, David E. ..... Rochester
‡ Culp, Clyde E. ..... Rochester
‡ Culp, Ormond S. ..... Rochester
Cummins, Ben M. .....Temple, TX
Cupps, Roger E. ..... Rochester

‡ Dahlin, David C. ..... Rochester
‡ Dale, Allan J. D. ..... Rochester
† Dankmyer, Frederick L. ..... Rochester
‡ Daugherty, Guy W. ..... Rochester
† David, Ronald B. ..... Rochester
Davidson, Allan D. .....Altus A.F.B., OK
Davidson, Horace B., Jr. ..... Washington, DC
Davignon, Jean ..... Montreal, Quebec
† Davis, Austin C. ..... Pompano Beach, FL
‡ Davis, George D. ..... Rochester
‡ Dearing, William H. ..... Rochester
‡ Decker, David G. ..... Rochester
† Deger, Grant E. ..... Rochester
DeLaus, Frank V., Sr. ..... Fort Riley, KS
DeRemee, Richard A. ..... Rochester
† Detenbeck, Lee C. ..... Rochester
‡ Devine, Kenneth D. ..... Rochester
‡ DeWeerd, James H. ..... Rochester
‡ Didier, Edward P. ..... Rochester
‡ Diessner, G. Roy ..... Rochester
† Dilley, John J. ..... Rochester
Dillman, Carl E., Jr. ..... Horsehead, NY
‡ Dines, David E. ..... Rochester
† Disney, Thomas F. ..... Rochester
‡ Divertie, Matthew B. ..... Rochester
† Dixon, Claude F. ..... Rochester
Dixon, George D. ..... Fargo, ND
‡ Dockerty, Malcolm B. ..... Rochester
† Dolan, Charles T. ..... Rochester
Donadio, James V., Jr. ..... Washington, DC
‡ Donoghue, Francis E. ..... Rochester
† Douglas, William W. ..... Rochester
‡ Douglass, Bruce E. ..... Rochester
‡ Doyle, James R. ..... Rochester
† Dozois, Roger R. ..... Rochester
† Drips, Della G. ..... Rochester
† Duane, Drake D. ..... Rochester
† Duval, David L. ..... Rochester
Duvoisin, George E. ..... Rochester
‡ Dyck, Peter J. ..... Rochester
‡ Dyer, John A. ..... Rochester

† Echols, William J. ..... Rochester
† Eckelberg, Merlyn E. ..... Rochester
† Edwards, Walter G., Jr. ..... Rochester
Ekberg, Norman L. .....Philadelphia, PA
‡ Elkins, Earl C. ..... Rochester
‡ Ellis, F. Henry, Jr. ..... Rochester

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Zumbro Valley Medical Society *(Continued)*

‡ Emmett, John L. ..... Rochester
† Emmons, Helen J. ..... Rochester
† Emmons, W. Frank ..... Rochester
‡ Emslander, Richard F. ..... Rochester
‡ Engel, Andrew G. ..... Rochester
Engels, Edward P. ..... Rochester
‡ Erich, John B. ..... Rochester
‡ Erickson, Donald J. ..... Rochester
† Eselius, Erik P. ..... Rochester
‡ Espinosa, Raul E. ..... Rochester
† Evans, Titus C., Jr. ..... Rochester
† Evarts, Arrah B. ..... Rochester

‡ Faber, John E. ..... Rochester
† Faber, John W. ..... Rochester
† Facer, George W. ..... Shawnee Mission, KS
‡ Fairbairn, John F., II ..... Rochester
Farrow, George M. ..... Rochester
‡ Faulconer, Albert, Jr. ..... Rochester
Fawcett, Kenneth J. ..... APO, San Francisco, CA
Fehrenbaker, Lawrence G. ..... Washington, DC
Feinberg, Jack H. ..... Mesa, AZ
Feldmann, Floyd M. ..... New York, NY
† Fenning, Robert L. ..... Rochester
‡ Ferguson, Richard H. ..... Rochester
‡ Ferris, Deward O. ..... Rochester
‡ Field, Charles A. ..... Rochester
†‡ Figi, Frederick A. ..... Rochester
† Finch, John E. ..... Rochester
† Fink, Lawrence H. ..... Rochester
† Finkelstein, Joel ..... Rochester
† Fish, Charles R. ..... Rochester
† Fisher, Darrell E. ..... Rochester
Fishman, Norton L. ..... Orlando, FL
†‡ Fluegel, John O. ..... Minneapolis
† Flick, Wm. F. ..... Rochester
Foley, Ralph B. ..... Ogden, UT
‡ Fontana, Robert S. ..... Rochester
† Forker, Alan D. ..... Rochester
† Foss, Edward L. ..... Condon, MT
† Foster, Thomas N., III ..... Rochester
‡ Foulk, William T., Jr. ..... Rochester
† Fowler, Franklin S., Jr. ..... Rochester
† Fox, John A. ..... Rochester
† Freel, Robert J. ..... Rochester
Freeman, F. Julian ..... FPO, San Francisco, CA
‡ Frethem, Allen A. ..... Rochester
† Fricke, Robert E. ..... Rochester
Fuller, Alen M. ..... Lawton, OK
† Fulton, Richard E. ..... Rochester
Furlow, William L. ..... Rochester
† Furman, Philip ..... Rochester

Galloway, Jackson R. ..... Alexandria, LA
†‡ Gambill, Carl M. ..... Rochester
‡ Gambill, Earl E. ..... Rochester
Garber, James J. ..... Rochester
Gasior, Robert M. ..... Chicago, IL
‡ Gastineau, Clifford F. ..... Rochester
† Gau, Gerald T. ..... London, England
Gedge, Stafford W. ..... Rochester
† Gentling, Peter A. ..... Rochester
‡ Geraci, Joseph E. ..... Rochester
† Giffin, Herbert Z. ..... Rochester
† Gilbaugh, James H., Jr. ..... Rochester
Gillis, Samuel P. ..... Birmingham, AL
† Goldman, Sherwin ..... Rochester
Gisvold, John J. ..... APO San Francisco, CA
† Goldner, John C. ..... Rochester
‡ Goldstein, Norman P. ..... Rochester
‡ Goldston, Edgar C. ..... Rochester
‡ Gomez, Manuel R. ..... Rochester
‡ Good, C. Allen, Jr. ..... Rochester
† Goren, Hershel ..... Rochester
Gorman, Columba A. ..... Rochester
‡ Gould, Allan B., Jr. ..... Rochester
† Gould, Ronauld J. ..... Rochester
Gracey, Douglas R. ..... Belleville, IL
† Graf, John A. ..... Rochester
‡ Green, Paul A. ..... Rochester
Greenberg, Eugene ..... Urbana, IL
‡ Greene, Laurence F. ..... Rochester
‡ Gregg, James A. ..... Rochester
#† Grimes, Allen E., Jr. ..... FPO, San Francisco, CA
†‡ Grindlay, John H. ..... Carbondale, CO
Groover, Robert V. ..... Rochester
‡ Gross, John B. ..... Rochester
Guillory, Joel R., Jr. ..... Lafayette, LA
Gulledge, Albert D. ..... Rochester

‡ Hagedorn, Albert B. ..... Rochester
‡ Hahn, Richard G. ..... Rochester
†‡ Haines, Samuel F. ..... Rochester
Hall, Jack W. ..... Rochester
‡ Hallberg, Olav E. ..... Rochester
‡ Hallenbeck, George A. ..... Rochester
‡ Hallermann, Franz J. ..... Rochester
† Ham, Oscar E., Jr. ..... Rochester
‡ Hanlon, David G. ..... Rochester
† Hanson, Jerome R. ..... Rochester
‡ Hanson, Norbert O. ..... Rochester
Hanton, Edward M. ..... St. Paul
† Hardy, Kent M. ..... Rochester
‡ Hargraves, Malcolm M. ..... Rochester
† Harrington, Stuart W. ..... Rochester
‡ Harris, Lloyd E. ..... Rochester
‡ Harrison, Edgar G., Jr ..... Rochester
Hathaway, David S. ..... Arlington, VA
Hartfield, James E., Jr. ..... Columbia, SC
Hartridge, Virginia B. ..... Rochester
† Hastings, John D. ..... Rochester
† Havig, Terrance A. ..... Rochester
‡ Hayles, Alvin B. ..... Rochester
Hays, James C. ..... New York, NY
† Heck, Frank J. ..... Rochester
†‡ Heidel, Werner ..... Cresskill, N. J.
Henderson, Darrell L. ..... Portsmouth, VA
‡ Henderson, Edward D. ..... Rochester
‡ Henderson, John W. ..... Rochester
‡ Henderson, Lowell L. ..... Rochester
† Henderson, R. Michael ..... Rochester
‡ Hepper, Norman G. ..... Rochester
‡ Hermans, Paul E. ..... Rochester
† Hertzler, Jerrad J. ..... Rochester
† Hewitt, Edith S. ..... Clearwater Beach, FL
† Hewitt, Richard M. ..... Clearwater Beach, FL
‡ Higgins, John A. ..... Rochester
Hilgers, Robert D. ..... Rochester
‡ Hill, John R. ..... Rochester
‡ Hill, Richard W. ..... Rochester
Hines, Edgar A., Jr. ..... Brevard, NC
Hoagland, H. Clark ..... San Antonio, TX
‡ Hodgson, John R. ..... Rochester
† Hoehn, James G. ..... Rochester
Hoffman, David L. ..... Rochester
Holbrook, Margaret A. ..... Rochester
Holland, C. R. ..... Rochester
‡ Hollenhorst, Robert W. ..... Rochester
‡ Holley, Keith E. ..... Rochester

Zumbro Valley Medical Society *(Continued)*

‡ Holman, Colin B. ..... Rochester
† Hood, Roderick P. ..... Rochester
‡ Hoover, Norman W. ..... Rochester
†‡ Horton, Bayard T. ..... Rochester
† Houston, Hal E., Jr. ..... Murray, KY
‡ Howard, Frank M., Jr. ..... Rochester
† Howell, John L. ..... Rochester
‡ Howell, Llewelyn P. ..... Rochester
Hudgins, Robert L. ..... Ft. Benning, GA
‡ Huizenga, Kenneth A. ..... Rochester
† Hummer, Wm. K. ..... Rochester
‡ Hunder, Gene G. ..... Rochester
†‡ Hunt, Arthur B. ..... Carmel, CA
‡ Hunt, James C. ..... Rochester

† Irwin, Jack C., Jr. ..... Rochester
† Isbell, Robert G. ..... Rochester
‡ Ivins, John C. ..... Rochester

‡ Jackman, Raymond J. ..... Rochester
† Jacobson, Stephen G. ..... Rochester
† Janda, Wayne E. ..... Rochester
† Janes, Donald R. ..... Wausau, WI
‡ Janes, Joseph M. ..... Rochester
† Jereb, John A. ..... Rochester
‡ Johnson, Carl E. ..... Rochester
† Johnson, David C. ..... Rochester
Johnson, Dexter W. ..... Great Falls, MT
‡ Johnson, Einer W., Jr. ..... Rochester
Johnson, Gerhard J. ..... Portsmouth, VA
† Johnson, Kenneth A. ..... Rochester
Johnson, L. Morris ..... Washington, DC
Johnson, Ralph B. ..... Lanesboro
† Jones, Harry F. ..... Rochester
Jones, H. Royden, Jr. ..... APO New York, NY
† Jordon, James J. ..... Rochester
† Joy, William B. ..... Rochester
‡ Joyce, John W. ..... Rochester
‡ Judd, Edward S. ..... Rochester
‡ Juergens, John L. ..... Rochester

‡ Kaese, Werner E. ..... Rochester
‡ Karnes, William E. ..... Rochester
† Kasher, R. Jerome ..... Rochester
‡ Kavanaugh, Gerald J. ..... Rochester
Katz, Elliott S. ..... Rochester
#‡Kazmier, Francis J. ..... Rochester
‡ Kearns, Thomas P. ..... Rochester
‡ Keating, F. Raymond ..... Rochester
‡ Keith, Haddow M. ..... Rochester
† Keith, Norman M. ..... Rochester
Kelalis, Panayotis P. ..... Rochester
‡ Kelly, Patrick J. ..... Rochester
‡ Kempers, Rogert D. ..... Rochester
† Kenefick, Thomas ..... Los Angeles, CA
‡ Kennedy, Charles C. ..... Rochester
† Kern, Eugene B. ..... Rochester
†‡ Kernohan, James W. ..... Rochester
‡ Kerr, Frederick W. L. ..... Rochester
Keys, Thomas F. ..... FPO San Francisco, CA
‡ Kiely, Joseph M. ..... Rochester
‡ Kierland, Robert R. ..... Rochester
Kincaid, O. W. ..... Rochester
† King, John E. ..... Rochester
‡ Kirby, Thomas J., Jr. ..... Rochester
Kirklin, John W. ..... Birmingham, AL
Klass, Donald W. ..... Rochester
Kline, Richard J. ..... Grand Forks, ND
‡ Knapp, Robert D., Jr. ..... Rochester
‡ Knutson, Lewis A. ..... Spring Grove
Koelsche, Giles A. ..... Rochester
† Kolb, Marvin O. ..... Rochester
‡ Kottke, Bruce A. ..... Rochester
† Krigsten, Eli J. ..... Rochester
‡ Krupp, Neal E. ..... Rochester
† Kubista, Theodore P. ..... Rochester
† Kullmann, George L. ..... Rochester
‡ Kvale, Walter F. ..... Rochester
‡ Kyle, Robert A. ..... Rochester
LaHood, Joseph J. ..... Long Beach, CA
‡ Lake, Clifford F. ..... Rochester
Lapp, N. LeRoy ..... Morgantown, WV
† Laroche, Gilles ..... Rochester
† Larson, Richard H. ..... Rochester
† Larson, Stephen L. ..... Rochester
† Lattin, John E., III ..... Rochester
† Laurnen, Edwin L. ..... Rochester
† Lavertu, Julien G. ..... Rochester
Lawrence, Van S. ..... Rochester
Layton, Donald D., Jr. ..... Rochester
† Leavelle, Dennis E. ..... Rochester
‡ Lee, Raymond A. ..... Rochester
‡ Lee, Robert E. ..... Rochester
Leonard, Paul F. ..... Rochester
‡ Lewis, Andrew J. ..... Rochester
‡ Lillie, John C. ..... Rochester
† Lindsay, Malcolm I., Jr. ..... Rochester
‡ Linman, James W. ..... Rochester
‡ Linscheid, Ronald L. ..... Rochester
‡ Lipscomb, Paul R. ..... Rochester
‡ Litin, Edward M. ..... Rochester
‡ Litzow, Thaddeus J. ..... Rochester
‡ Lofgren, Eric P. ..... Rochester
‡ Lofgren, Karl A. ..... Rochester
‡ Logan, George B. ..... Rochester
† Long, Richard J. ..... Quebec, Canada
‡ Love, J. Grafton ..... Rochester
† Ludes, Bernard F. ..... Rochester
‡ Lundborg, Richard O. ..... Rochester
Lynch, Miles W. ..... Mt. Prospect, IL
‡ Lynn, Hugh B. ..... Rochester

‡ McBean, James B. ..... Rochester
McCarthy, Laurence ..... Honolulu, HI
† McConahay, David R. ..... Rochester
‡ McConahey, William M., Jr. ..... Rochester
‡ McGill, Douglas B. ..... Rochester
‡ McGoon, Dwight C. ..... Rochester
‡ McIlrath, Donald C. ..... Rochester
McKenna, Charles H. ..... Chicago, IL
‡ McPherson, James R. ..... Rochester
McRoberts, Jerry W. ..... Bremerton, WA
‡ MacCarty, Collin S. ..... Rochester
† MacDonald, Charles J. ..... Rochester
MacLean, Alexander R. ..... Rochester
† MacKenzie, Kenneth R. ..... Rochester
†‡ Magath, Thomas B. ..... Rochester
Magid, Gail A. ..... Santa Cruz, CA
† Magnant, Henry ..... Rochester
Magness, John L. ..... Rochester
‡ Maher, Frank T. ..... Rochester
Mair, Douglas D. ..... Goldsboro, NC
‡ Maldonado, Jorge E. ..... Rochester
‡ Malkasian, George D. ..... Rochester
‡ Mankin, Harold T. ..... Rochester
Marcoux, J. Paul ..... Bethesda, MD
‡ Martens, Theodore G. ..... Rochester
‡ Martin, Gordon M. ..... Rochester

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‡ Martin, Harold R. ..... Rochester
‡ Martin, John T. ..... Rochester
‡ Martin, Maurice J. ..... Rochester
‡ Martin, William J. ..... Rochester
† Martyn, David T. ..... Rochester
† Masson, Duncan M. ..... Rochester
† Masson, James C. ..... Rochester
‡ Masson, James K. ..... Rochester
Mastan, Peter F. ..... APO New York, NY
‡ Mathieson, Don R. ..... Rochester
Maupin, Roger A. ..... San Francisco, CA
Mayne, John G. ..... Rochester
†‡ Mayo, Charles W. ..... Rochester
Meyer, Melvin E. ..... Rochester
‡ Merritt, Wallace A. ..... Rochester
† Mertens, Benny F. ..... Rochester
† Mess, Charles F. ..... Rochester
† Meyerding, Henry W. ..... Rochester
Miller, Alfred ..... Rochester
† Miller, Donald R. ..... Rochester
Miller, John W., Jr. ..... Louisville, KY
‡ Miller, R. Drew ..... Rochester
‡ Miller, Ross H. ..... Rochester
‡ Millikan, Clark H. ..... Rochester
‡ Mills, Stephen D. ..... Rochester
† Mockert, Thomas, Jr. ..... Rochester
Moeller, Henry G., Jr. ..... Charleston, SC
†‡ Moersch, Fred P. ..... Ft. Lauderdale, FL
†‡ Moersch, Herman J. ..... Rochester
‡ Moertel, Charles G. ..... Rochester
‡ Moffitt, Emerson A. ..... Rochester
‡ Molnar, George D. ..... Rochester
†‡ Montgomery, Hamilton ..... Rochester
Moore, Gordon L., II ..... Rochester
† Morgan, Stephan S. ..... Rochester
Mori, Hideo ..... Grand Meadow
‡ Morlock, Carl G. ..... Rochester
‡ Morrow, George W., Jr. ..... Rochester
Morse, Robert M. ..... Rochester
‡ Mulder, Donald W. ..... Rochester
‡ Muller, Sigfrid A. ..... Rochester
Mussey, Mary E. ..... Rochester
† Myers, George H., Jr. ..... Rochester
‡ Myers, Thomas, T. ..... Rochester
† Myers, Thomas T., III ..... Rochester
† Nadeau, Claude ..... Trois-Riveres, Que., Canada
† Nathan, Fred F. ..... Rochester
‡ Neault, Roger W. ..... Rochester
† Nelson, Audrey M. ..... Rochester
Nelson, J. Phillip ..... Millington, TN
† Nelson, Rodger K. ..... Rochester
† Nettles, Joe L. ..... Rochester
Newcomer, Albert D. ..... San Diego, CA
‡ Nichols, Donald R. ..... Rochester
† Nobrega, Fred T. ..... Rochester
† Nolan, Alfred C. ..... Rochester
O'Connell, Edward J. ..... March A.F.B., CA
† O'Donnell, Kevin T. ..... Southfield
† O'Sullivan, Michael B. ..... Rochester
Oberstein, Barry J. ..... Rantoul, IL
† Obetz, Samuel W. ..... Rochester
† Odyniec, Norman ..... Rochester
† Oels, Helen C. ..... Rochester
† Okeson, Gyman C. ..... Rochester
‡ Olsen, Arthur M. ..... Rochester
Olson, Grant E. ..... West Concord
† Olson, Neal R. ..... Rochester
‡ Ongley, Patrick A. ..... Rochester
Onofrio, Burton M. ..... Rochester
† Onsgard, L. Kenneth ..... St. Petersburg, FL
† Onstad, Thomas A. ..... Rochester
‡ Opitz, Joachim L. ..... Rochester
‡ Osmundson, Philip J. ..... Rochester
‡ Owen, Charles A., Jr. ..... Rochester
† Patrolero, Peter C. ..... Rochester
‡ Palumbo, Pasquale J. ..... Rochester
‡ Paris, Jaime ..... Rochester
† Parker, Joseph C., Jr. ..... Rochester
‡ Parker, Robert L. ..... Rochester
† Parkhill, Edith M. ..... Rochester
‡ Parkin, Thomas W. ..... Rochester
Parsons, William R. ..... Portland, OR
‡ Paulson, John A. ..... Rochester
Payne, Robert A. ..... Athens, GA
† Payne, Stanley, R. ..... Rochester
‡ Payne, W. Spencer ..... Rochester
Peacock, William F., III ..... Littleton, CO
† Pease, Gertrude L. ..... Rochester
*†‡Pemberton, John deJ. ..... Rochester
‡ Perry, Harold O. ..... Rochester
‡ Peters, Gustavus A. ..... Rochester
Petersen, Magnus C. ..... Rochester
Peterson, Hamlet A. ..... Rochester
‡ Peterson, Lowell F. A. ..... Rochester
Peterson, Richard A. ..... APO Seattle, WA
‡ Peyla, Thomas L. ..... Rochester
Pierre, Robert V. ..... Rochester
‡ Pilling, Loran F. ..... Rochester
† Pingree, George C. ..... Rochester
† Plummer, Alan L. ..... Rochester
† Pluth, James R. ..... Rochester
Polley, Howard F. ..... Rochester
‡ Pool, T. Lloyd ..... Rochester
Poston, Lawrence M. ..... Caledonia
† Potter, Myron T., II ..... Carbondale, IL
‡ Pratt, Joseph H., Jr. ..... Rochester
‡ Priestley, James T. ..... Rochester
Pruitt, Raymond D. ..... Rochester
‡ Pugh, David G. ..... Rochester
‡ Pulec, Jack L. ..... Rochester
‡ Purnell, Don C. ..... Rochester
‡ Ralston, Donald E. ..... Rochester
†‡ Randall, Lawrence M. ..... Rochester
‡ Randall, Raymond V. ..... Rochester
† Rawls, William E. ..... Houston, TX
Redfield, Nicholas P. ..... Ft. Rucker, AL
† Reed, John H., Jr. ..... Rochester
‡ Reese, David F. ..... Rochester
Reeves, Bradford F. ..... APO 96377
‡ Reiher, Jean ..... Rochester
† Reilly, William F., Jr. ..... Rochester
‡ Reitemeier, Richard J. ..... Rochester
‡ ReMine, William H., Jr. ..... Rochester
‡ Restall, Charles J. ..... Rochester
† Retzlaff, John A. ..... Rochester
Rhoton, Albert L., Jr. ..... Rochester
Riley, Fenwick C. ..... Rochester
‡ Risser, Alden F. ..... Stewartville
Robertson, Dennis M. ..... Rochester
‡ Rogne, William G. ..... Spring Grove
† Roland, Charles Jr. ..... Rochester
Rome, Howard P. ..... Rochester
‡ Rooke, Edward D. ..... Rochester
‡ Rosenow, Edward C., III ..... Rochester
‡ Rosevear, John W. ..... Rochester

Zumbro Valley Medical Society *(Continued)*

‡ Ross, James V., Jr. ..... Rochester
‡ Rovelstad, Randolph A. ..... Rochester
† Roy, Paul H. J. ..... Rochester
Rubenstein, Mark M. ..... San Francisco, CA
†‡ Rucker, Charles W. ..... Rochester
† Rulfs, David M., Jr. ..... Rochester
‡ Rushton, Joseph G. ..... Rochester
Russell, Thomas J. ..... Barksdale, LA
† Rydell, Ralph E. ..... Rochester
†‡ Rynearson, Edward H. ..... Rochester
Sabens, James A. ..... Fort Campbell, KY
Sakulsky, Stephen B. ..... APO San Francisco, CA
‡ Salassa, Robert M. ..... Rochester
‡ Sander, Frank V., Jr. ..... Rochester
Sanderson, David R. ..... Rochester
† Sandok, Burton A. ..... Rochester
Sanfelippo, Peter M. ..... APO San Francisco, CA
‡ Sauer, William G. ..... Rochester
Sawtell, Robert R. ..... Rochester
Sayre, George P. ..... Rochester
‡ Scanlon, Paul W. ..... Rochester
‡ Schattenberg, Thomas T. ..... Rochester
Schirger, Alexander ..... Rochester
† Schlein, Allen P. ..... Rochester
† Schnur, Paul L. ..... Rochester
† Schoen, Roland F., Jr. ..... Rochester
‡ Schoenfield, Leslie J. ..... Rochester
‡ Scholz, Donald A. ..... Rochester
† Scofield, Edward L. ..... Rochester
‡ Scudamore, Harold H. ..... Rochester
† Sebald, John R. ..... Rochester
‡ Sedlack, Richard E. ..... Rochester
‡ Seldon, Thomas H. ..... Rochester
† Service, Frederick J. ..... Rochester
‡ Sessler, Alan D. ..... Rochester
† Seybold, Marjorie E. ..... Rochester
‡ Sheps, Sheldon G. ..... Rochester
‡ Shick, Richard M. ..... Rochester
‡ Siekert, Robert G. ..... Rochester
† Silverman, Louis F. ..... Houston, TX
‡ Silverstein, Murray N. ..... Rochester
‡ Simons, John N. ..... Rochester
‡ Simonton, Kinsey M. ..... Rochester
† Simpson, Thomas E. ..... Rochester
‡ Skaug, Harold M. ..... Chatfield
† Skolnick, Judah L. ..... Rochester
‡ Slocumb, Charles H. ..... Rochester
Smith, David E. ..... Washington, DC
Smith, David L. ..... San Diego, CA
† Smith, Frederick L. ..... Rochester
Smith, George R. ..... Lafayette, LA
† Smith, Harry L. ..... Rochester
‡ Smith, Lucian A. ..... Rochester
† Smith, Max ..... Rochester
‡ Smith, Ralph E. ..... Rochester
‡ Smith, Reginald A. ..... Rochester
Smith, Robert J., Jr. ..... Beaverton, OR
† Snider, James H. ..... Rochester
‡ Sones, Donald A. ..... Rochester
‡ Soule, Edward H. ..... Rochester
‡ Spencer, Robert J. ..... Rochester
‡ Spiekerman, Ralph E. ..... Rochester
‡ Spittell, John A., Jr. ..... Rochester
‡ Sprague, Randall G. ..... Rochester
† Spring, Donald A. ..... Rochester
† Stacey, Richard R. ..... Rochester
† Stambuk, Berigoj K. ..... Rochester
† Starkey, Thomas A. ..... Rochester
†‡ Stauffer, Maurice H. ..... Rochester
† Stauffer, Richard N. ..... Rochester
Stecker, Raymond H. ..... APO N. Y., NY
‡ Steinhilber, Richard M. ..... Rochester
Stenseth, Jon H. ..... APO New York, NY
† Sterling, William A. ..... Rochester
† Stevens, John C. ..... Rochester
#‡Stewart, James R. ..... El Paso, TX
‡ Stickney, J. Minott ..... Rochester
‡ Stillwell, G. Keith ..... Rochester
‡ Stilwell, George G. ..... Rochester
Stobbe, Juergen A. ..... APO New York, NY
‡ Stroebel, Charles F., Jr. ..... Rochester
† Strong, Cameron G. ..... Rochester
† Stubbs, Samuel E. ..... Rochester
† Suiter, Ronald D. ..... Rochester
Summerskill, William H. ..... Rochester
‡ Svien, Hendrik J. ..... Rochester
‡ Symmonds, Richard E. ..... Rochester
† Tachovsky, Thomas J. ..... Rochester
† Tancredi, Robert G. ..... Rochester
‡ Taswell, Howard F. ..... Rochester
Tauxe, Welby N. ..... Rochester
† Teem, Martin V., Jr. ..... Rochester
Teller, Richard M. ..... Rochester
Thomas, Juergen E. ..... Rochester
Thompson, Dennis P. ..... China Lake, CA
† Thompson, Gershorn J. ..... Rochester
† Thompson, Wayman J., Jr. ..... Rochester
‡ Thurber, Deloran L. ..... Rochester
† Tiffany, Joseph C. II ..... Rochester
†‡ Tillisch, Jan H. ..... Rochester
‡ Tinkham, Robert G. ..... Rochester
‡ Titus, Jack L. ..... Rochester
† Todd, David W. ..... Rochester
† Toft, Thomas V. ..... Rochester
† Tompkins, Richard B. ..... Rochester
Trautmann, James C. ..... Rochester
† Turner, Eugene F. ..... Rochester
Turner, Norman S. ..... No. Arlington, NJ
Tyce, Francis A. ..... Rochester
‡ Uihlein, Alfred ..... Rochester
‡ Underdahl, Laurentius O. ..... Rochester
‡ Utz, David C. ..... Rochester
† Van Dellen, Richard G. ..... Rochester
‡ Van Herik, Martin ..... Rochester
‡ Vaughn, Louis D. ..... Rochester
†‡ Veneziale, Carlo M. ..... Madison, WI
‡ Verby, John E. ..... Rochester
† Vermillion, Stanley E. ..... Rochester
Vesper, Lee J. ..... Cincinnati, OH
† Viles, Peter H. ..... Rochester
Virnig, Hildegard J. ..... Caledonia
† Vittands, Ingvars J. ..... Rochester
‡ Wagoner, Richard D. ..... Rochester
Wahman, Robert E. ..... Duluth
† Wakim, Khalil G. ..... Rochester
‡ Wallace, Robert B. ..... Rochester
† Waller, Robert R. ..... Rochester
† Walls, Joseph T. ..... Rochester
† Walsh, William E. ..... Rochester
†‡ Walters, Waltman ..... Rochester
‡ Ward, Louis E. ..... Rochester
† Washington, John A. ..... Rochester
†‡ Watkins, Charles H. ..... Sun City, Az.
† Watkins, Phillip C. ..... Rochester
† Watterson, Wm. M. ..... Rochester
Weaver, Arthur L. ..... Denver, CO

Continued on Next Page

Zumbro Valley Medical Society *(Continued)*

† Weber, William F. ..... Rochester
† Webster, Kirk H. ..... Rochester
‡ Weed, Lyle A. ..... Rochester
‡ Weeks, Richard E. ..... Rochester
‡ Weidman, William H. ..... Rochester
† Weier, Thomas E. ..... Rochester
† Weiland, Louis H. ..... Rochester
Weingart, Jon L. ..... Ft. Leonard Wood, MO
†‡ Weir, James F. ..... Rochester
† Weisberg, Martin G. ..... Rochester
‡ Welch, John S. ..... Rochester
Wellek, Mark A. ..... APO New York, NY
‡ Wellman, William E. ..... Rochester
Wellner, Theodore O. ..... Rochester
‡ Wente, Harold A. ..... Rochester
† Westbrook, Philip R. ..... Rochester
‡ Westrup, John E. ..... Lanesboro
Wharton, William P. ..... Rochester
‡ Whisnant, Jack P. ..... Rochester
† White, Stewart A. ..... Rochester
† White, William L. ..... Rochester
† Whyte, Thomas R. ..... Rochester
† Whittaker, Lorin D., Jr. ..... Rochester
† Wiegand, Stewart E. ..... Rochester
Wilber, Robert D. ..... Ft. Knox, KY
Williams, David Eugene ..... Lehore, W. Pakistan
‡ Williams, Tiffany J. ..... Rochester
† Williamson, Kenneth R. ..... Rochester
† Willius, Fredrick A. ..... Rochester
Wilson, David F. ..... Washington, DC
‡ Wilson, Robert B. ..... Rochester
‡ Wilson, Viktor O. ..... Rochester
Wiltsie, John C. ..... Rochester
‡ Winkelmann, Richard K. ..... Rochester
‡ Witten, David M. ..... Rochester
‡ Wollaeger, Eric E. ..... Rochester
Wood, Lloyd T. ..... Rochester
† Woods, John E. ..... Rochester
‡ Woolner, Lewis B. ..... Rochester
‡ Worthington, John W., Jr. ..... Rochester
† Wotychu, Edward B. ..... Rochester
Wright, Charles L., Jr. ..... Worchester, MA
Wychulis, Adam R. ..... Phoenixville, PA
† Wyman, John B. ..... Marshfield, WI
Yackel, Douglas B. ..... San Francisco, CA
Yalowitz, Philip A. ..... Rochester
‡ Yoss, Robert E. ..... Rochester
† Youman, Joseph D., III ..... Rochester
‡ Young, Henry H. ..... Rochester
Zacharski, Leo R. ..... Ft. Hayes, OH

ALPHABETIC ROSTER

Key to Symbols

\# Service
* Deceased
† Life, Associate, Affiliate and Resident
¶ Honorary

A

Aaro, Leonard A. ..... Rochester
Abraham, Arden L. ..... Duluth
Abrams, Alexander, Jr. ..... St. Paul
Abramson, Burton I. ..... Minneapolis
Abramson, Michael B. ..... Oakland, CA
Abramson, Milton ..... Minneapolis
Abullarade, Jose A. ..... Minneapolis
Abuzzahab, Faruk S. ..... Minneapolis
Adair, Albert F., Jr. ..... St. Paul
Adams, Brandon L. W. ..... Minneapolis
Adams, Harold R. ..... St. Paul
Adams, Patrick J. ..... Shakopee
Adams, Richard I. ..... Minneapolis
Adcock, Leon L. ..... Minneapolis
Addy, Edward R. ..... Gilbert
Adkins, C. Douglas ..... Minneapolis
Adkins, James T. ..... Coon Rapids
Adson, Martin A. ..... Rochester
Affeldt, Daniel E. ..... Kasson
Aga, John H. ..... Brainerd
Agustsson, Hreidar ..... Minneapolis
Ahern, Eugene E. ..... Minneapolis
† Ahlfs, Jacob J. ..... Ft. Lauderdale, FL
Ahlstrom, Robert C. ..... Braham
Ahmann, David L. ..... Rochester
Ahola, Kenneth E. ..... Hibbing
Ahrens, Curtis F. ..... Duluth
Ahrens, Robert M. ..... St. Paul
Akins, Willard M. ..... Red Wing
Alari, Heino ..... Excelsior
Albrecht, Raymond J. ..... St. Paul
Alcorn, William J. ..... Wabasso
Alden, Charles W. ..... Sauk Rapids
Alden, John F. ..... St. Paul
Aldrete, Joaquin S. ..... Ft. Gordon, GA
Alexander, Harlan A. ..... Minneapolis
Aling, Charles A. ..... Minneapolis
Allen, James R. ..... Minneapolis
Allen, John H. ..... Montevideo
Allen, Raymond A. ..... Rochester
Allison, David D. ..... Litchfield
Allocco, Dominic J. ..... APO San Francisco, CA
Alter, Milton ..... Minneapolis
† Altman, Robert L. ..... Rochester
† Altnow, Hugo O. ..... Coral Gables, FL
Alton, Donald G. ..... St. Paul
Amatuzio, Donald S. ..... Minneapolis
† Amberg, Samuel ..... Rochester
Amerongen, Werner W. ..... St. Paul
† Amos, David A. ..... Muskegon, MI
Amren, Don P. ..... Minneapolis
Anderegg, Alfred F. ..... St. Paul
Andersen, Howard A. ..... Rochester
Andersen, James G. ..... Minneapolis
Anderson, Arden O. ..... Brainerd
Anderson, Arnold S. ..... Minneapolis
Anderson, Ben H. ..... Minneapolis
Anderson, Chester A. ..... Hector
Anderson, Chester A. ..... Madison
Anderson, David M. ..... Minneapolis
Anderson, David P., Jr. ..... Austin
Anderson, David W. ..... St. Paul
*† Anderson, Edward D. ..... Vaud, Switzerland
Anderson, Ernest R. ..... Minneapoilis
Anderson, Frank J. ..... Minneapolis
Anderson, Franklin C. ..... Owatonna
Anderson, Harold J. ..... Austin
Anderson, James J. ..... St. Paul
Anderson, James M. ..... Duluth
Anderson, Jo E. ..... LeSueur
Anderson, John A. ..... Minneapolis
Anderson, John W. ..... Blue Earth
† Anderson, Karl W. ..... Excelsior
Anderson, Margaret C. ..... St. Paul
† Anderson, Mark J. ..... Sun City, AZ
Anderson, Markham J., Jr. ..... Rochester
Anderson, Milton W. ..... Rochester
Anderson, Oscar D. ..... Mankato
† Anderson, Richard E. ..... Willmar
Anderson, Richard W. ..... St. Paul
Anderson, Richard W. ..... Minneapolis
Anderson, Roger E. ..... Minneapolis
Anderson, Roger L. ..... Minneapolis
Anderson, Russell H. ..... Virginia
Anderson, Thomas P. ..... Minneapolis
Anderson, U. Schuyler ..... Edina
Anderson, W. Robert ..... Minneapolis
Anderson, Waldo P. ..... Buffalo
Anderson, Wallace E. ..... Minneapolis
Anderson, Wallace R. ..... Minneapolis
† Anderson, Werner W. ..... Cincinnati, OH
Anderson, William H. ..... Minneapolis
Anderson, William T. ..... Minneapolis
Andre, James C. ..... Grand Rapids
† Andreassen, Einar C. ..... Minneapolis
Andreassen, Rolf L. ..... Minneapolis
Andresen, Karl d'A ..... Minneapolis
Ankner, Frank J. ..... Minneapolis
Anonsen, Richard E. ..... Minneapolis
Anselment, Lois A. ..... Excelsior
† Antolak, Stanley J., Jr. ..... Minneapolis
Antonow, Arthur M. ..... Virginia
† Arends, Archibald L. ..... Minneapolis
Arey, Stuart Lane ..... Minneapolis
Arhelger, Stuart W. ..... Minneapolis
† Arkin, Charles R. ..... Rochester
Arlander, Clarence E. ..... Minneapolis
Arling, Leonard S. ..... Minneapolis
† Armbruster, Robert M. ..... Rochester
Arms, James J. ..... Minneapolis
Armstrong, Byron H. ..... Minneapolis
Armstrong, Ralph S. ..... Winnebago
† Arndt, Harry W. ..... Detroit Lakes
Arnesen, John F. ..... Owatonna
Arnesen, Paul M. ..... Mankato
Arneson, Arthur I. ..... Morris
† Arnold, Ann W. ..... Minneapolis

Arnold, Gordon B. ..... Cupertino, CA
Arnold, Thomas B. ..... Minneapolis
Arny, Frederick P. ..... St. Paul
Aruguete, Alayne ..... Sandstone
Aruguete, Jose ..... Sandstone
Arzt, Philip K. ..... St. Paul
† Ashby, Thomas M. ..... Rochester
Ashmore, Herbert C. ..... St. Paul
Asp, Donald S. ..... Milaca
Asta, Joseph J. ..... Duluth
† Athens, Alvin G. ..... Santa Barbara, CA
Atmore, William G. ..... Duluth
Auerbach, Arthur M. ..... Hartford, CT
Aufderheide, Arthur C. ..... Duluth
† Auger, Armand J. ..... Putnam, CT
Aughenbaugh, John W. ..... Minneapolis
Aulick, Ernest J. ..... Paynesville
Auran, David B. ..... St. Paul
Aurelius, J. Richards ..... St. Paul
Ausman, Duane R. ..... St. Paul
† Aust, John C. ..... Minneapolis
Austrian, Sol ..... St. Paul
Autrey, William A. ..... St. Cloud
Avant, Robert F. ..... Minneapolis
Azad, A. M. ..... Minneapolis

B

Baab, Robert O. ..... Crookston
Babb, Frank S. ..... St. Paul
Bach, Jerome M. ..... St. Paul
Backus, Byron C. ..... Cloquet
Backus, Lloyd B. ..... Cloquet
Backus, Reno W. ..... Nopeming
† Badeaux, George I. ..... Brainerd
Bader, J. L. ..... Slayton
Baggenstoss, Archie H. ..... Rochester
Baggenstoss, Osmond J. ..... Minneapolis
Bagley, Charles M. ..... Duluth
Bagley, Elizabeth C. ..... Duluth
Bagley, Russell W. ..... Minneapolis
Bah, Merle C. ..... St. Paul
Bahn, Robert C. ..... Rochester
Baich, Velemir M. ..... Coleraine
Bair, Hugo L. ..... Rochester
Baird, Raymond L. ..... Harmony
¶ Bajec, Dusan ..... Poljane, Yugoslavia
Baken, Melvin P. ..... Minneapolis
Baken, Melvin P., Jr. ..... Minneapolis
Baker, Abe B. ..... Minneapolis
Baker, C. Camak ..... Minneapolis
Baker, Chilton R., Jr. ..... Herlong, CA
† Baker, Daniel R. ..... St. Paul
Baker, George S. ..... Rochester
† Baker, Harry R. ..... Hayfield
Baker, Hillier L., Jr. ..... Rochester
Baker, James A. ..... Ft. Campbell, KY
Baker, Jeannette L. ..... Fergus Falls
Baker, Milton E. ..... Minneapolis
Baker, Norman H. ..... Fergus Falls
Bakke, Arnold C. ..... Minneapolis
Bakkila, Henry E. ..... Duluth
Balce, Regino V. ..... St. Paul
Balderson, Robert P. ..... Grand Rapids
* Baleisis, Peter ..... Minneapolis
Balfour, William M. ..... Lawrence, KS
Balkin, Samuel G. ..... Minneapolis
Balkins, John W. ..... Minneapolis
Ballantine, Jerome J. ..... St. Cloud
Balmer, Albert I. ..... Duluth
Balogh, Charles J. ..... Minneapolis
Bancroft, Burton R., Jr. ..... St. Cloud
Banfield, Frederick ..... Rochester
† Bank, Harry E. ..... Minneapolis
Banner, Edward A. ..... Rochester
Banovetz, John D. ..... Minneapolis
Baraga, Anthony R. ..... Hibbing
Barbarisi, Charles F. ..... Mankato
† Barbee, Charles W., Jr. ..... Rochester
Barber, Tracy E. ..... Austin
Bardon, Richard ..... Duluth
† Barer, Malvin ..... Oakland, CA
Barker, John D. ..... Duluth
† Barker, Nelson W. ..... Rochester
† Barnes, Arlie R. ..... Rochester
Barnes, Richard E. ..... Aurora
Barnett, Arthur J. ..... Foley
Barnett, Robert M. ..... Minneapolis
† Barney, Leon A. ..... Duluth
Barno, Alex ..... Minneapolis
Barr, Lowell C. ..... Albert Lea
Barr, Lowell W. ..... Albert Lea
Barr, Maxwell M. ..... Minneapolis
Barr, Robert N. ..... Minneapolis
Barrett, Earl E. ..... Duluth
Barrett, Patrick J. ..... Minneapolis
Barron, Jesse J. ..... Minneapolis
† Barron, Mosses ..... Beverly Hills, CA
Barry, George J. ..... Minneapolis
Barry, Maurice J., Jr. ..... Rochester
Bartholdt, H. Peter ..... Cook
Bartholomew, Lloyd G. ..... Rochester
Bartness, John E. ..... Albert Lea
Bartzen, Peter J. ..... Duluth
Basinger, Harold P. ..... Windom
† Basinger, Homer P. ..... Windom
Bastron, James A. ..... Rochester
Batdorf, B. Niles ..... Mankato
Bateman, Clarence V. ..... Fergus Falls
Bauer, Eugene L. ..... St. Paul
Bauer, Paul G. ..... Faribault
Bauman, John C. ..... Foley
† Baumgartner, Carl J., Jr. ..... Rochester
Baumgartner, Florian H. ..... Albany
Bayley, E. Covell ..... Lake City
Bayrd, Edwin D. ..... Rochester
Beabout, John W. ..... Rochester
Beach, Northrop ..... Minneapolis
Beahrs, Oliver H. ..... Rochester
Bealka, Neil M. ..... Stillwater
Bean, Charles N. ..... Waconia
Beard, Archibald H., Jr. ..... Minneapolis
Beaton, J. Gordon ..... Northfield
† Bechamps, Gerald J. ..... Rochester
Beck, Charles J. ..... No. St. Paul
† Beckenbaugh, Robert D. ..... Rochester
† Becker, Arnetta M. ..... Treasure Island, FL

Becker, Frederic T. ..... Duluth
Beckering, Gerrit ..... Edgerton
† Beckering, Raymond E. ..... Rochester
Beckering, Roland G. ..... Edgerton
Becklund, Roger W. ..... Minneapolis
Beckman, Donovan L. ..... St. Paul
Beek, Harvey O. ..... St. Paul
Beeman, John A. ..... Minneapolis
Beer, John J. ..... St. Paul
Behr, Orlo K. ..... Crookston
Beirstein, Samuel ..... Minneapolis
Beiswanger, Richard H. ..... Minneapolis
Belau, Paul G. ..... Rochester
Belcher, Royden A. ..... Little Falls
Bell, Donald C. ..... Minneapolis
Bell, Harry M. Jr. ..... Duluth
† Bell, Richard A. ..... Rochester
Bellomo, James ..... St. Paul
Bellomo, John ..... Fairmont
Bellville, Titus P. ..... Minneapolis
Belshe, Joseph ..... St. Cloud
Belz, Reinmar ..... St. Paul
Belzer, Meyer S. ..... Minneapolis
Bendel, William L., Jr. ..... Minneapolis
Bender, James H. ..... Brainerd
Bendix, Lester H. ..... Annandale
† Benedict, William L. ..... Rochester
† Benell, Otto E. ..... Britt
Benepe, James L. ..... St. Paul
Benesh, Louis A. ..... Minneapolis
Benjamin, Edwin G. ..... Minneapolis
Benjamin, Harold G. ..... Minneapolis
Benjamin, Richard D. ..... Minneapolis
Benjamin, Robert B. ..... Minneapolis
Benjamin, Walter G. ..... Pipestone
Bennett, Clayton J. ..... Rochester
* Benson, A. H. ..... Little Falls
Benthack, Elaine M. ..... Minneapolis
Bentz, Herman D. ..... Anoka
Bepko, Marie K. (Mrs. Puumala) ..... Cloquet
† Berdez, George L. ..... Duluth
Berestka, Stephen J. ..... Minneapolis
Berg, Arnold M. ..... Thief River Falls
Berg, Clinton C. ..... Excelsior
† Bergan, Otto ..... Clinton
Bergan, Robert O. ..... Duluth
Berge, Harry L. ..... Mora
Berge, Kenneth G. ..... Rochester
Berger, Alex G. ..... Minneapolis
Berger, Phil R. ..... St. Cloud
† Bergh, Allen V. ..... Rochester
Bergh, George S. ..... Minneapolis
Bergh, Solveig M. ..... Minneapolis
Berglund, Alvin E. ..... Cambridge
Berglund, Eldon B. ..... Minneapolis
† Bergman, Oscar B. ..... St. James
Bergstrom, Ralph W., Jr. ..... Maple Plain
Bergquist James R. ..... Minneapolis
† Berkman, John M. ..... Rochester
Berkwitz, Nathaniel J. ..... Minneapolis
Berman, David A. ..... Minneapolis
Berman, Reuben ..... Minneapolis
Bernatz, Philip E. ..... Rochester
Berner, Herbert W., Jr. ..... Worthington
† Bernier, Merrill J. ..... No. St. Paul
Bernstein, Irving C. ..... Minneapolis
† Bernstein, William C. ..... St. Paul
Berris, Harold ..... Minneapolis
Berry, Ronald N. ..... Minneapolis
Berzins, Rainis ..... Minneapolis
† Bessesen, Alfred N. ..... Minneapolis
Beuning, John B. ..... St. Cloud
Bevis, William D. ..... Minneapolis
† Bianco, Anthony J. ..... Vero Beach, FL
Bianco, Anthony J., Jr. ..... Rochester
Bickel, William H. ..... Rochester
Bickford, Joyce A. ..... Rochester
† Bieger, R. Cyril ..... Rochester
Bieter, Raymond N. ..... Minneapolis
† Bieter, Thomas G. ..... St. Paul
† Bigelow, Charles E. ..... Dodge Center
Bigler, Earl E. ..... Perham
Bigler, Ivan E. ..... Perham
Bilka, Paul J. ..... Minneapolis
Billings, Harry H. ..... Red Wing
Billman, Herbert R. ..... Minneapolis
† Bilstad, James M. ..... Rochester
Binder, Manuel R. ..... Minneapolis
† Binet, Henry E. ..... Grand Rapids
Bingham, George C. ..... Olivia
Birkebak, Roland C. ..... St. Paul
Birkemeyer, Eugene J. ... Mountain Home AFB, ID
Birkey, Thomas G. ..... Montevideo
Bisel, Harry F. ..... Rochester
Bissinger, Lester L. ..... Brainerd
Bittick, Wilbur H. ..... Minneapolis
Black, B. Marden ..... Rochester
Black, Earl J. ..... White Bear Lake
Black, William A. ..... New Ulm
Blackard, Clyde E. ..... Minneapolis
Blackburn, Henry W., Jr. ..... St. Paul
Blackwell, Leonard H. ..... Hutchinson
Blake, Allan J. ..... Hopkins
Blake, James A. ..... Hopkins
Blake, Paul S. ..... Minneapolis
Blaw, Michael E. ..... Minneapolis
Bloch, Henry S. ..... Minneapolis
Bloedel, Traugott J. ..... Osseo
Blomberg, Robert D. ..... Minneapolis
Blomberg, William R. ..... St. Paul
† Blondin, Claude ..... Rochester
Bloom, David ..... Minneapolis
Bloom, Joseph ..... Silver Bay
Bloom, Norman B. ..... Minneapolis
† Blossman, Robert C. ..... Rochester
Blumberg, Henry B. ..... St .Paul
Blumenthal, Malcolm N. ..... Minneapolis
Blumer, Arlo R. ..... Albert Lea
Boardman, Dalmon V. ..... Winona
Boardman, William J. ..... Minneapolis
† Bock, Rolland A. ..... St. Paul
Boecker, Bernhard ..... Duluth
Bofenkamp, Benjamin ..... Minneapolis
Bofenkamp, Ferdinand W. ..... Luverne
Bohn, Donald G. ..... Minneapolis
Boies, Lawrence R. ..... Hopkins
Boies, Lawrence R., Jr. ..... Wayzata
Boline, Clifford A. ..... Battle Lake
Bologna, Camillo V. ..... Moorhead
Bolstad, Owen C. ..... Reno, NV
Bolt, Donald A. ..... Minneapolis
Bolz, J. Arnold ..... Grand Rapids
Boman, Paul G. ..... Duluth
† Boman, Peter L. ..... Rochester
† Bonebrake, Robert A. ..... Rochester
Bonello, Frank J. ..... St. Paul
Bonner, John L. ..... Grand Rapids
Boody, George ..... Cambridge
Boone, Ervin S. ..... Luverne
Borgerson, Arthur H. ..... Long Prairie

Borman, Chauncey N. ..... Minneapolis
Borowicz, Leonard A. ..... Minneapolis
† Boseker, Edward H. ..... Newport Beach, CA
Bosland, Howard G. ..... Willmar
† Bosland, Jon H. ..... Rochester
Bosley, Patrick ..... Balaton
Botting, Arthur J. ..... APO San Francisco, CA
† Bottolfson, B. T. ..... Moorhead
† Bouma, Lewis R. ..... St. Paul
Bouquet, Bertram J. ..... Wabasha
Bouthilet, Florence J. ..... Minneapolis
† Bower, Philip J. ..... Rochester
† Bowers, Frank R. ..... Rochester
Bowers, Gordon ..... Minnetonka
Bowers, Robert N. ..... Lake City
Bowie, E. J. Walter ..... Rochester
Bowlin, Paul F. ..... Minneapolis
† Boyd, Allen S., Jr. ..... Rochester
Boyd, David A., Jr. ..... Rochester
Boyd, Frank E. ..... Pipestone
Boyer, Samuel H. ..... Duluth
† Boyer, Stanley W. ..... Rochester
Boyle, Francis J. ..... Springfield
† Boynton, Ruth E. ..... Miami, FL
Boysen, Herbert ..... Madelia
Boyum, Allan J. ..... Marshall
Bozanich, Milosh S. ..... St. Cloud
† Braasch, William F. ..... Rochester
† Brabec, Paul F. ..... Hastings
Brace, Ray I. ..... Clinton
Bradley, Jeanne B. ..... Minneapolis
Bradley, John G. ..... Minneapolis
Bradley, William E. ..... Minneapolis
Brainard, John B. ..... St. Paul
Brand, Frank R. ..... Columbia, MO
† Brand, William A. ..... Redwood Falls
Brandenburg, Robert O. ..... Rochester
Brandt, Henry E. ..... Minneapolis
† Branham, Donald S. ..... Hastings
Bransford, Paul W. ..... Minneapolis
Bratholdt, James W. ..... Watertown
† Bratrud, Edward ..... Alexandria
† Bratrude, Earl J. ..... Hopkins
Brattensborg, Henry J. ..... St. Cloud
Brauer, William W. ..... Minneapolis
Braun, Ohrmundt C. ..... Grand Rapids
Braun, Rene ..... Minneapolis
Bray, Philip N. ..... Duluth
Breitenbucher, Robert B. ..... Minneapolis
Brekke, Harvey J. ..... Minneapolis
Brende, Joel O. ..... Littlefork
Brenk, Paul E. ..... Detroit Lakes
Brennan, Joseph G. ..... Minneapolis
Bretzke, Carl O. ..... Hutchinson
Briggs, John F. ..... St. Paul
Briggs, Thomas G. ..... White Bear Lake
Brigham, Charles F., Jr. ..... St. Cloud
Brill, Alice K. ..... Minneapolis
Brink, Adlai A. ..... Baudette
Brink, Donald M. ..... St. Peter
† Brinkman, James F. ..... Rochester
Briones, Bienvenido R. ..... Hopkins
Broadbent, James C. ..... Rochester
Broadie, Thomas E. ..... St. Paul
Brockway, Roger W. ..... Grand Rapids
Brodhun, John C. ..... Rochester
† Brodie, Walter D. ..... St. Paul
Broker, Henry M. ..... St. Cloud
Broman, Harold R., Jr. ..... No. St. Paul
Brooker, Warren J. ..... Duluth
† Brookler, Kenneth H. ..... Rochester
† Brooks, Charles N. ..... Wayzata
† Brown, Alex E. ..... Brandenton, FL
Brown, Arnold L. ..... Rochester
Brown, Christopher J. ..... St. Paul
Brown, Cyrus C., Jr. ..... Duluth
Brown, Donald J. ..... Ventnor, NJ
Brown, Frank T. ..... St. Cloud
Brown, Glenn W. ..... Halstad
Brown, Hector M. ..... St. Paul
Brown, Henry A. ..... Rochester
Brown, James E., Jr. ..... St. Paul
Brown, James P. ..... St. Paul
Brown, Joe R. ..... Rochester
Brown, John H. ..... Minneapolis
Brown, John M. ..... St. Paul
† Brown, Patrick M. ..... Rochester
† Brown, Philip W. ..... Rochester
Brown, Philip W., Jr. ..... Rochester
Brown, Russell T. ..... Browerville
Brown, William D. ..... Minneapolis
Brown, William D., Jr. ..... Minneapolis
Bruhl, Heinz H. ..... Faribault
Brusegard, James F. ..... Red Wing
Bryar, George E. ..... Chicago, IL
† Bucchiere, John J., Jr. ..... Rochester
Bucher, Foster D. ..... Starbuck
Buchstein, Harold F. ..... Minneapolis
† Buck, Frederick H. ..... Shakopee
Buckley, Joseph J. ..... Minneapolis
Buckley, Robert P. ..... Duluth
Buesgens, Ralph H. ..... Waterville
Bugby, Robert D. ..... Minneapolis
Bugenstein, Robert H. ..... Minneapolis
† Buie, Louis A. ..... Rochester
Buie, Louis A., Jr. ..... Minneapolis
Buirge, Raymond E. ..... Minneapolis
Bulinski, Theodore J. ..... St. Paul
Bulluck, Matthew H. ..... Duluth
Bundt, Robert E. ..... Minneapolis
Bunker, Bevan W. ..... Anoka
Buran, David J. ..... Minneapolis
Burbank, Mahlon K. ..... Rochester
Buresh, Kenneth L. ..... Owatonna
† Burge, Kelmar M. ..... Rochester
Burgert, E. O., Jr. ..... Rochester
Burich, Harry F. ..... Rochester
Burke, Edmund C. ..... Rochester
Burkholder, Dayton D. ..... Anoka
Burklund, Edwin C. ..... St. Paul
Burlingame, David A. ..... St. Paul
Burman, Richard E. ..... Aitkin
Burmeister, Richard O. ..... St. Paul
Burnett, Joseph W. ..... New Ulm
Burnham, Wesley H. ..... Minneapolis
† Burns, Catherine ..... Excelsior
Burns, Floyd M. ..... Milan
Burns, John M. ..... St. Paul
† Burns, M. A. ..... Milan
Burseth, Edgar C. ..... Mora
Burton, J. Richard ..... St. Paul
Burton, Robert C. ..... Rochester
Burton, Thomas P. ..... Minneapolis
Buscemi, Michael F. ..... Belleville, NJ
Bush, Robert P. ..... St. Paul
† Bush, Stephen T. ..... Rochester
*† Busher, Herbert H. ..... St. Paul

Butler, John K. ..... Cloquet
Butt, Hugh R. ..... Rochester
† Butzer, John A. ..... Mankato
Butzer, John F. ..... Mankato
Byrne, William J. ..... St. Paul
† Byron, Robert S. ..... Rochester

C

Cable, Morris L. ..... Minneapolis
Cabot, Clyde M. ..... Minneapolis
Cain, Clark L. ..... St. Paul
Cain, James C. ..... Rochester
Cain, James H. ..... Alexandria
Cairns, Robert J. ..... Redwood Falls
† Caldwell, Joseph G. ..... Rochester
† Calhoun, Frank W. ..... Albert Lea
† Cali, Robert W. ..... Rochester
Calin, S. Hartley ..... Minneapolis
Callahan, John A. ..... Rochester
† Cameron, Isabell L. ..... Minneapolis
Cameron, John H. ..... Clovis, NM
Camp, Ray J. ..... Madison
Campaigne, Robert J. ..... Duluth
Campbell, Denis V. ..... Minneapolis
Campbell, Donald C. ..... Rochester
Campbell, John C. ..... Albert Lea
Campbell, Malcolm K. ..... Rochester
Campbell, Orwood J. ..... Minneapolis
Canine, James L. ..... So. St. Paul
Cant, Wilbur F. ..... Red Wing
† Cantwell, William F. ..... International Falls
Caplan, Leslie ..... Minneapolis
Card, William H. ..... Minneapolis
Cardle, George E. ..... Brainerd
Cardle, James G. ..... Minneapolis
Cardle, John B. ..... Minneapolis
Carey, James B., Jr. ..... Minneapolis
Carey, Lewis S. ..... St. Paul
Carlander, Lester W. ..... Minneapolis
Carlon, Donald L. ..... Moorhead
Carlson, Carl E. ..... Alexandria
Carlson, Charles V. ..... Mound
† Carlson, Erik E. ..... Hopkins
Carlson, Harley C. ..... Rochester
Carlson, Homer J. ..... Pelican Rapids
Carlson, John V. ..... Westbrook
Carlson, Lawrence ..... Minneapolis
Carlson, Lloyd E. ..... Worthington
Carlson, Robert G. ..... Anoka
Carlson, Russel E. ..... Stillwater
Carlson, Vernon J. ..... Moorhead
Carney, Francoise ..... Rochester
Caron, Robert P. ..... Minneapolis
Carr, David T. ..... Rochester
Carr, William J. ..... Minneapolis
Carrier, Thomas C. ..... Minneapolis
† Carrington, Stewart G. ..... Rochester
Carroll, John J. ..... Winsted
Carryer, Haddon M. ..... Rochester
Carter, Earl T. ..... Rochester
Carthey, Frank J. ..... New Ulm
Caspers, Carl G. ..... Minneapolis
Catlin, Theodore J. ..... Buffalo
Cauble, Charles F. ..... Minneapolis
† Cavanor, Frank T. ..... Minneapolis
Cavert, H. Mead ..... Minneapolis
Cecil, James W. ..... Marysville, CA
Cedarleaf, Cherry B. ..... White Bear Lake
Ceder, Elmer T. ..... Minneapolis
Cella, Joseph A. ..... Minneapolis
Ceplecha, Stanley F. ..... Redwood Falls
Cerino, Lawrence E. ..... Pompano Beach, FL
Cervenka, Charles F. ..... New Prague
Cesnik, Robert J. ..... Sauk Rapids
Chadbourn, Wayne A. ..... Minneapolis
Chalgren, William S. ..... Mankato
Challman, S. Alan ..... Minneapolis
Chandler, William M. ..... Great Lakes, IL
† Chatterton, Carl C. ..... St. Paul
Chedister, Charles R. ..... Minneapolis
Chermak, Francis G. ..... International Falls
Chesler, Merrill D. ..... Minneapolis
Child, Sherman B. ..... Minneapolis
Childs, Donald S., Jr. ..... Rochester
† Chiroff, Richard T. ..... Rochester
Chisholm, Tague C. ..... Minneapolis
Chou, Shelley N. ..... Minneapolis
Christensen, Clarence H. ..... Duluth
Christensen, Eli E. ..... Winona
Christensen, Llewellyn E. ..... Minneapolis
Christensen, Norman A. ..... Rochester
Christenson, Carl E. ..... Clinton
Christenson, Leland R. ..... Maple Plain
Christgau, Roger A. ..... Minneapolis
Christian, William L. ..... Austin
Christiansen, Harold A. ..... Jackson
Chung, Stanley M. K. ..... Biloxi, MS
Chunn, Stanley S. ..... Willmar
Church, Gerald E. ..... Two Harbors
Cich, John A. ..... W. St. Paul
Ciriacy, Edward W. ..... Ely
Clagett, O. Theron ..... Rochester
Clapp, Hubert D. ..... Crookston
† Clark, Edward C. ..... San Francisco, CA
Clark, Elizabeth A. (Mrs. Halbert) ..... Duluth
† Clark, Harry B. ..... St. Cloud
Clark, Ivan T. ..... Duluth
† Clark, Leslie W. ..... Manchester, IA
Clark, Malcolm D. ..... Minneapolis
Clark, Robert S. ..... Minneapolis
Clark, W. Bruce ..... St. Paul
† Clarke, Dean T. ..... Faribault
Clarke, John W. ..... Waconia
Clay, Lyman B. ..... Minneapolis
Cleaves, Wm. D. ..... Sauk Centre
Clifford, George W. ..... Alexandria
† Clifton, Theodore A. ..... Hollywood, FL
Closuit, Frederick C. ..... Aitkin
Cochrane, Byron B. ..... St. Paul
Cochrane, Ray F. ..... Minneapolis
Coddon, Walter D. ..... St. Paul
Code, Charles F. ..... Rochester
Coder, Donald M. ..... Portsmouth, VA
Cody, D. Thane ..... Rochester
Coe, John I. ..... Minneapolis

Cohen, Bernard A. ..... Minneapolis
Cohen, Ephraim B. ..... Minneapolis
Cohen, Henry W. ..... Wayzata
† Cohen, Manley ..... Rochester
Cohen, Sumner S. ..... Minneapolis
Colby, Malcolm Y., Jr. ..... Rochester
† Colby, Woodard L. ..... St. Paul
Cole, George A. ..... Albert Lea
Cole, James S. ..... Minneapolis
Cole, Wallace H. ..... St. Paul
Coleman, John B. ..... St. Paul
† Coleman, Robert L. ..... Rochester
Coleman, Thomas P. ..... Minneapolis
Coles, Douglas T. ..... Rochester
Coll, James J. ..... Duluth
† Collins, Arthur N. ..... Duluth
† Collins, Roger T. ..... Rochester
† Collison, Robert W. ..... Rochester
Colman, Edward L. ..... Fergus Falls
Colton, Roger S. ..... St. Paul
Comfort, Thomas H. ..... Minneapolis
Conley, Francis W. ..... Duluth
Conley, Robert H. ..... Mankato
Conlin, F. Dixon ..... Minneapolis
Conlon, Daniel C. ..... Minneapolis
Connolly, Coleman J. ..... St. Paul
Connolly, Daniel C. ..... Rochester
Connolly, Joseph P. ..... West St. Paul
† Connor, Charles E. ..... St. Paul
† Connor, David G. ..... Minneapolis
† Cook, C. Kenneth ..... St. Paul
Cook, Edward N. ..... Rochester
Coombs, Carl H. ..... Cass Lake
Cooper, Charles C. ..... Moose Lake
Cooper, Herbert A. ..... Marysville, CA
Cooper, John P. ..... Minneapolis
Cooper, Robert R. ..... Minneapolis
Cooper, Talbert ..... Rochester
Cope, Hershel B. ..... Virginia
Corbin, Kendall B. ..... Rochester
Corcoran, James R. ..... New York, NY
† Corniea, Albert D. ..... Minneapolis
Correa, Dale H. ..... Minneapolis
Corrigan, Cyril J. ..... Rochester
Cortez, Daniel P. ..... Minneapolis
* Cosgriff, James A. ..... Olivia
Cosgriff, James A., Jr. ..... Olivia
† Cotton, Gerald E. ..... Rochester
Cottor, Robert E. ..... Duluth
Coulter, Harold E. ..... Minneapolis
† Countryman, Roger S. ..... Saratoga, CA
Courteau, Robert D. ..... Onamia
Coventry, Markham B. ..... Rochester
Coventry, William D. ..... Duluth
Covey, Kenneth W. ..... Moorhead
Cowan, Donald W. ..... Minneapolis
Cowan, George M. ..... Duluth
Cowger, Robert C. ..... Farmington
Cox, Russell L. ..... Estherville, IA
Coy, Douglas J. ..... Grand Rapids
Craig, David M. ..... St. Paul
Craig, M. Elizabeth ..... Minneapolis
Cram, Barclay M. ..... St. Paul
† Cranmer, Richard R. ..... Minneapolis
Cranston, Robert W. ..... Minneapolis
† Creasman, John P. ..... Rochester
Creevy, Charles D. ..... Minneapolis
Creps, James R. ..... Duluth
Cronwell, Bernhard J. ..... Austin
Crow, Earl R. ..... Minnetonka
Crow, George M. ..... International Falls
† Crowder, Bennett, L., II ..... Ft. Campbell, KY
Crowley, James H. ..... St. Paul
Crowley, Leonard V. ..... Minneapolis
Crudo, Vincent D. ..... St. Paul
Crum, Arthur Z. ..... St. Paul
† Crump, James W. ..... St. Paul
† Crutchfield, Susan E. ..... Fairchild AFB, WA
Cullado, Andrionico F. ..... Minneapolis
Cullen, Robert M. ..... Elmore
† Culligan, David E. ..... Rochester
Culligan, John A. ..... St. Paul
Culligan, Leo C. ..... Minneapolis
Culp, Clyde E. ..... Rochester
Culp, Ormond S. ..... Rochester
Culver, Lucian G. ..... St. Paul
Cumming, Edward D. ..... St. Paul
Cumming, Robert J. ..... St. Cloud
Cummins, Ben M. ..... Temple, TX
Cundy, Donald T. ..... Minneapolis
Cupps, Roger E. ..... Rochester
Curran, John P. ..... Anoka
* Curtis, Rauen A. ..... Le Center
Cushing, Richard T. ..... Minneapolis
† Cutts, George ..... Minneapolis

D

Daehlin, Rolf ..... Fergus Falls
Dagg, Earl ..... Thief River Falls
Daggett, Donald R. ..... Minneapolis
† Dahl, Elmer O. ..... Minneapolis
Dahl, James C. ..... Minneapolis
† Dahl, John A. ..... Minneapolis
Dahlin, David C. ..... Rochester
Dahlquist, La Rue V. ..... Pipestone
Dale, Allan J. D. ..... Rochester
Dale, Les N. ..... Hastings
† Daly, Alfred E. ..... Burnsville
D'Angio, Giulio J. ..... Minneapolis
† Daniel, Donald H. ..... Minneapolis
Danielson, Lennox ..... Litchfield
† Dankmyer, Frederick L. ..... Rochester
Danyluk, Michael ..... Minneapolis
Dargay, Cyril P. ..... Minneapolis
Daugherty, Guy W. ..... Rochester
† Daumann, Roy E. ..... Minneapolis
David, Reuben ..... Hopkins
† David, Ronald B. ..... Rochester
Davidson, Allan D. ..... Altus AFB, OK
Davidson, Duane J. ..... Thief River Falls
Davidson, Horace B. ..... Washington, DC
Davignon, Jean ..... Montreal, Quebec
† Davis, Austin C. ..... Pompano Beach, FL
Davis Edward V. ..... St. Paul
Davis, Eunice A. ..... Bismarck, ND
Davis, George D. ..... Rochester
† Davis, Jay C. ..... Pompano Beach, FL

† Davis, Lloyd T. ..... Wadena
Davis, Luther F. ..... Wadena
Davis, Michael W. ..... APO New York, NY
Davis, Raymond D. ..... Stockton, CA
Davis, Thomas H. ..... Minneapolis
Davis, William I. ..... Moose Lake
Dawson, James R. ..... St. Paul
Dawson, Lorin D. ..... Worthington
Dawson, Walter J., Jr. ..... Minneapolis
Dearing, William H. ..... Rochester
Deason, Keith B. ..... Chisago City
Decker, Charles H. ..... St. Paul
Decker, David G. ..... Rochester
Dedeker, Kenneth L. ..... Wayzata
Degallier, Daniel ..... Winona
† Deger, Grant E. ..... Rochester
Delahunty, John R. ..... Red Wing
DeLaus, Frank V. ..... Ft. Riley, KS
Delmore, John L. ..... Roseau
Delzell, Allen W. ..... Minneapolis
De Marais, Lloyd C. ..... Hibbing
Demo, Robert A. ..... Albert Lea
DeMordaunt, Paul R. ..... Blackfoot, ID
*† Derauf, Benjamin I. ..... St. Paul
Derauf, Donald E. ..... St. Paul
Derechin, William ..... St. Paul
DeRemee, Richard A. ..... Rochester
Desai, B. J. ..... Worthington
† Detenbeck, Lee C. ..... Rochester
Deters, Donald C. ..... St. Paul
Deutsch, Robert J. ..... Duluth
* Devereaux, Thomas J. ..... Wayzata
Devine, Kenneth D. ..... Rochester
† de Werd, Daniel L. ..... Kansas City, MO
deWerd, Robert W. ..... Owatonna
De Weerd, James H. ..... Rochester
Deweese, Wilford J. ..... Bemidji
Dewey, Donald H. ..... Owatonna
Diamond, Robert A. ..... Minneapolis
Dickson, Franklin H. ..... Proctor
Didier, Edward P. ..... Rochester
Diefenbach, Eugene J. ..... Minneapolis
† Diehl, Harold S. ..... New York, NY
Dierker, Heinrich A. ..... Minneapolis
† Diessner, Ardell W. ..... Redwood Falls
Diessner, Grant R. ..... Rochester
† Diessner, Henry D. ..... Minneapolis
Dietrich, Donald E. ..... Duluth
Dille, Donald E. ..... Litchfield
Dillenburg, Cyril J. ..... Crookston
† Dilley, John J. ..... Rochester
Dillman, Carl E., Jr. ..... Columbia, SC
Dines, David E. ..... Rochester
Disney, Thomas F. ..... Rochester
Dittrich, Raymond ..... St. Paul
† Divertie, Matthew B. ..... Rochester
† Dixon, Claude F. ..... Rochester
Dixon, George D. ..... Fargo, ND
Doan, Robert E. ..... Wayzata
Dobbs, Richard L. ..... Duluth
Dobler, Manfred G. ..... Ely
Dobson, Mervin W. ..... Mankato
Docherty, John A. ..... Edina
Dockerty, Malcolm B. ..... Rochester
Docksey, John W. ..... Willmar
Dodds, William C. ..... Detroit Lakes
Dodson, Albertus F. ..... Brainerd
Doebler, Myron I. ..... Mora
Doherty, Elmer M. ..... New Prague
Dokken, James H. ..... Windom
† Dolan, Charles T. ..... Rochester
Dolmage, George H. ..... St. Paul
Doman, Victor W. ..... Lakefield
Doms, Vernon A. ..... Elbow Lake
Donadio, James V., Jr. ..... Washington, DC
Donaldson, Charles S. ..... St. Cloud
Donatelle, Edward P. ..... Minneapolis
Donoghue, Francis E. ..... Rochester
Donovan, Daniel L. ..... New Brighton
Dooley, Robert T. ..... St. Paul
† Dorge, Richard I. ..... Minneapolis
Dornbach, Robert A. ..... Minneapolis
Dorsey, George C., Jr. ..... Minneapolis
Dorsey, William E. ..... Minneapolis
Doscherholmen, Alfred ..... Minneapolis
Dougan, Jerome W. ..... Minneapolis
† Douglas, William W. ..... Rochester
Douglass, Bruce E. ..... Rochester
Douglass, Jesse E. ..... Cannon Falls
† Doxey, Gilbert L. ..... Minneapolis
Doyle, James R. ..... Rochester
† Dozois, Roger R. ..... Rochester
Dredge, Thomas E. ..... Minneapolis
Dredge, Thomas E., Jr. ..... Minneapolis
Drexler, Charles J. ..... Duluth
Drexler, George W. ..... Blue Earth
Drill, Frederick E. ..... Minneapolis
Drill, Herman E. ..... Hopkins
† Drips, Della G. ..... Rochester
† Duane, Drake D. ..... Rochester
Dubois, Julian F. ..... Sauk Centre
Duff, Edwin R. ..... Minneapolis
Duffy, John C. ..... Minneapolis
Dummer, Donald J. ..... New Brighton
Duncan, Donald A. ..... Minneapolis
Duncan, James W. ..... Moorhead
Dunlap, Earl H. ..... Minneapolis
Dunn, Robert C. ..... St. Paul
Dunstan, Paul L. ..... Willmar
Dupont, Joseph A. ..... Excelsior
Durkin, John L. ..... St. Paul
Duryea, Marbry ..... Minneapolis
Duryea, Willis M. ..... Minneapolis
Duryea, Willis M., Jr. ..... Minneapolis
† Duthoy, Everette J. ..... St. Paul
† Duval, David L. ..... Rochester
Duvall, Arndt J., III ..... Minneapolis
Duvoisin, George E. ..... Rochester
Dvorak, Benjamin A. ..... Minneapolis
Dwan, Paul F. ..... Minneapolis
† Dworsky, Samuel D. ..... Minneapolis
Dwyer, John J. ..... Duluth
Dyck, Peter J. ..... Rochester
Dyer, John Allen ..... Rochester
Dyrdal, Paul J. ..... St. Paul
Dysterheft, Adolf F. ..... Gaylord
Dziubinski, Emil H. ..... St. Cloud

E

Earl, George A. ..... St. Paul
Earl, John R. ..... St. Paul
Earl, Stephan H. ..... Minneapolis
Eaton, David B. ..... Worthington

Eberley, Tobe S. ..... Benson
Ebert, Richard B. ..... Minneapolis
† Echols, William J. ..... Rochester
Eckdale, John E. ..... Marshall
† Eckelberg, Merlyn E. ..... Rochester
Eckerly, Jean R. ..... Minneapolis
Eckman, Philip F. ..... Duluth
Eckman, Philip L. ..... Duluth
Eckman, Ralph J. ..... Duluth
Eder, Walter P. ..... Minneapolis
Edmondson, Hugh A., Jr. ..... Minneapolis
Edwards, J. Willard ..... St. Paul
Edwards, Jesse E. ..... St. Paul
Edwards, Lloyd G. ..... St. Paul
Edwards, Richard B. ..... St. Paul
Edwards, Thomas J. ..... St. Paul
† Edwards, Walter G., Jr. ..... Rochester
Edwin, Russell L. ..... North Mankato
Eelkema, Herman H. ..... St. Paul
Efteland, Myles E. ..... Minneapolis
Egge, Sanford G. ..... Albert Lea
Eginton, Charles T. ..... Fargo, ND
† Ehrenberg, Claude J. ..... Boca Raton, FL
Ehrlich, S. Paul ..... Minneapolis
Eich, Matthew A. ..... Minneapolis
Eichelberger, Dale L. ..... Willmar
Eichenlaub, John E. ..... Minneapolis
Eichhorn, Edmund P., Jr. ..... Minneapolis
† Eichler, George R. ..... Akron, OH
Eide, O. A. ..... Hancock
† Eiden, Vera M. ..... Afton
Eilers, Vincent E. ..... St. Paul
Eilers, William B. ..... Redwood Falls
Eisenbeis, C. F. ..... Mankato
Eisenman, Walter ..... Hibbing
† Eisenstadt, David H. ..... Minneapolis
Eisenstadt, William S. ..... Minneapolis
Eitel, George D. ..... Minneapolis
Ekberg, Norman Lee ..... Philadelphia, PA
† Ekdale, Robert A. ..... Menlo Park, CA
Eklund, Carl D. ..... Duluth
*† Elias, Frank J. ..... Duluth
Elkins, Earl C. ..... Rochester
Ellertson, Leonard M. ..... Albert Lea
Ellinger, Albert J. ..... Willmar
Ellingson, Richard B. ..... Minneapolis
Elliott, Harold J. ..... Hayfield
Ellis, Earl W. ..... Elgin
Ellis, F. Henry, Jr. ..... Rochester
Ellis, Ronald W. ..... St. Paul
Ellison, Evan S. ..... Minneapolis
† Ellison, Frank E. ..... Monticello
Ellwood, Paul M., Jr. ..... Minneapolis
Emanuel, Karl W. ..... Duluth
Emerson, Edward C. ..... St. Paul
Emerson, Edwin E. ..... Osakis
Emmett, John L. ..... Rochester
† Emmons, Helen J. ..... Rochester
Emmons, Robert W. ..... St. Paul
† Emmons, Wm. F. ..... Rochester
Emond, Joseph S. ..... Farmington
Emond, Joseph S., Jr. ..... Minneapolis
Emslander, Richard F. ..... Rochester
Endress, Edward K. ..... St. Paul
Engberg, Edward J. ..... Faribault
Engel, Andrew G. ..... Rochester
Engel, Joseph P. ..... Minneapolis
†* Engelhart, Peter C. ..... Minneapolis
Engels, Edward P. ..... Rochester
Engelstad, Wendell P. ..... Virginia
England, Rodney W. ..... St. Paul
Englund, Elvin F. ..... Minneapolis
† Engstrand, Oscar J. ..... Minneapolis
Engstrom, E. Duane ..... Minneapolis
Engstrom, George F. ..... St. Peter
Engstrom, Robert B. ..... Mankato
Engwall, Richard L. ..... Minnetonka
Enroth, Oscar E. ..... St. Paul
* Eppard, Raymond M. ..... Cloquet
Erdal, Ove A. ..... Columbia, MO
Erich, John B. ..... Rochester
Erickson, Alvin O. ..... Long Prairie
Erickson, Clifford O. ..... Minneapolis
Erickson, Donald J. ..... Rochester
Erickson, Myron E. ..... Minneapolis
Erickson, Reuben ..... Minneapolis
Erickson, Robert L. ..... Rosemount
Erickson, Vernon D. ..... Grand Rapids
† Erickson, William D. ..... Rochester
† Ericson, Swan ..... Los Angeles, CA
Erlanson, A. Cornell ..... St. Paul
† Ersek, Robert A. ..... Minneapolis
Ersfeld, Murray P. ..... St. Paul
† Eselius, Erik P. ..... Rochester
Esensten, Sidney ..... Minneapolis
Espelien, Alan D. ..... St. Cloud
Espinosa, Raul E. ..... Rochester
Estrem, Ralph L. ..... Fergus Falls
Estrem, Robert D. ..... Fergus Falls
Ettinger, Milton G. ..... Minneapolis
Etzwiler, Donnell D. ..... Minneapolis
Eustermann, John J. ..... Mankato
Evans, Edward T. ..... Minneapolis
Evans, Leslie M. ..... Sauk Rapids
† Evans, Titus C., Jr. ..... Rochester
† Evarts, Arrah B. ..... Rochester
Evensta, John B. ..... Grand Rapids
Everhart, Clarence E., Jr. ..... Minneapolis
Everhart, Francis J. ..... Minneapolis
Evison, Emerson O. ..... Duluth
Ewens, George B. ..... Virginia

F

Faber, John E. ..... Rochester
† Faber, John W. ..... Rochester
† Facer, George W. ..... Shawnee Mission, KS
† Fahr, George E. ..... Minneapolis
Fairbairn, John F., II ..... Rochester
† Fallon, Virgil T. ..... Minneapolis
Falls, John L. ..... Red Wing
Farber, Lawrence A. ..... Minneapolis
Farkas, John V. ..... St. Paul
Farley, Harrison H. ..... Minneapolis
Farrell, T. Edwin ..... Minneapolis
Farrow, George M. ..... Rochester
Fasbender, Herman T. ..... Hastings
Faul, Bennie C. ..... Worthington
Faulconer, Albert, Jr. ..... Rochester
Fawcett, Arthur M. ..... Renville
Fawcett, Keith R. ..... Duluth
Fawcett, Kenneth J. ..... APO San Francisco, CA

Fedor, Robert D. ..... Litchfield
Fee, John G. ..... St. Paul
† Feeney, John M. ..... Excelsior
Fehrenbaker, Lawrence G. ..... Washington, DC
Feigal, David W. ..... Wayzata
Feigal, William M. ..... Fairmont
Feinberg, Jack H. ..... Meza, AZ
Feinberg, Philip ..... Minneapolis
Feinberg, Samuel B. ..... Minneapolis
Feinstein, Julius Y. ..... Minneapolis
Felder, Davitt A. ..... St. Paul
Feldmann, Floyd M. ..... New York, NY
Felion, Arthur J. ..... St. Paul
Fellows, Manley F. ..... Duluth
† Fenger, Ejvind P. K. ..... Chanhassen
† Fenning, Robert L. ..... Rochester
Fenske, Arnold W. ..... Winona
Ferguson, John N. ..... St. Paul
Ferguson, Richard H. ..... Rochester
* Ferguson, William C. ..... Walnut Grove
Fernandez, Rafael F., Jr. ..... Minneapolis
Ferrell, Clarence R. ..... Grand Rapids
Ferris, Deward O. ..... Rochester
Fesenmaier, Otto B. ..... Los Angeles, CA
† Fesler, Harold H. ..... Eugene, OR
Fetzek, Albert D. ..... Minneapolis
Feuling, John C. ..... Duluth
Field, Charles A. ..... Rochester
Field, Charles W. ..... Hopkins
Fifer, Ellen Z. ..... St. Paul
Fifer, William R. ..... Minneapolis
Fifield, Malcolm M. ..... Duluth
† Figi, Frederick A. ..... Rochester
Filiatrault, L. J. ..... Coon Rapids
Filipovich, Orest N. ..... Minneapolis
† Finch, John E. ..... Rochester
Fingerman, David L. ..... Minneapolis
Fink, Daniel L. ..... St. Paul
† Fink, Lawrence H. ..... Rochester
Fink, Leo W. ..... Minneapolis
Fink, Robert J. ..... Minneapolis
† Fink, Walter H. ..... Minneapolis
Finkelnburg, William O. ..... Winona
† Finkelstein, Joel ..... Rochester
Finlayson, Richard E. ..... Minneapolis
† Fischer, John R. ..... Parkway, MO
*† Fischer, Mario M. ..... Duluth
Fischer, Robert F. ..... St. Paul
† Fish, Charles R. ..... Rochester
Fisher, Dan W. ..... St. Paul
† Fisher, Darrell E. ..... Rochester
Fisher, Don H. ..... Minneapolis
Fisher, Isadore I. ..... Minneapolis
Fishman, Norton L. ..... Orlando, FL
Fisketti, Henry ..... Duluth
Fitch, Charles G. ..... Worthington
Fitzsimons, William E. ..... Brainerd
† Flancher, Leon H. ..... Detroit Lakes
Flannery, Hubert F. ..... St. Paul
Fleming, Dean S. ..... Minneapolis
Flentje, Dale E. ..... Mankato
† Flick, Wm. F. ..... Rochester
Fliehr, Richard R. ..... Minneapolis
Flinn, James B. ..... Redwood Falls
Floersch, Adrian J. ..... Owatonna
Flom, Reynold P. ..... St. Paul
Flom, Robert S. ..... St. Paul
Flora, George C. ..... Minneapolis
Florence, David W. ..... Robbinsdale
Florine, Martin C. ..... Madison Lake
Flory, William D. ..... Minneapolis
† Fluegel, John O. ..... Minneapolis
Flynn, Bernard F. ..... Hibbing
Flynn, Louis L., Jr. ..... St. Paul
Flynn, Robert A. ..... St. Paul
Foderick, John W. ..... Hastings
Foderick, Peter P. ..... Hallock
† Fogarty, Charles W. ..... St. Paul
Fogelberg, Emil J. ..... St. Paul
Foker, Leslie W. ..... Minneapolis
Foley, Ralph B. ..... Ogden, UT
Foley, Robert R. ..... Minneapolis
Foley, Wm. A. ..... Minneapolis
Folsom, Louis B. ..... Minneapolis
Fontana, Robert S. ..... Rochester
Forbes, Edward F. ..... Minneapolis
† Ford, Burton C. ..... Marshall
Ford, W. Harold ..... Hopkins
† Forker, Alan D. ..... Rochester
Forsythe, James R. ..... St. Paul
Fortier, George M. A. ..... Little Falls
Fortier, Rene G. ..... Mankato
† Foss, Edward L. ..... Condon, MT
Foster, Orley W. ..... Minneapolis
† Foster, Thomas N. III ..... Rochester
Foulk, William T., Jr. ..... Rochester
† Fowler, Franklin, Jr. ..... Rochester
Fox, James Rogers ..... Minneapolis
† Fox, John A. ..... Rochester
Fox, LeRoy J. ..... St. Paul
† Franchere, Frederick W. ..... Lake Crystal
Francis, David W. ..... Morristown
Frane, Donald B. ..... Minneapolis
Frane, Gerald T. ..... Minneapolis
Franklin, Gordon W. ..... Northome
Fredericks, George M. ..... Minneapolis
† Frederickson, Alice C. ..... Willmar
† Freel, Robert J. ..... Rochester
Freeman, Charles D., Jr. ..... St. Paul
Freeman, Craig W. ..... Minneapolis
Freeman, Donald H. ..... Mankato
Freeman, Donald W. ..... St. Louis Park
Freeman, F. Julian ..... La Grange, GA
French, Bayard T. ..... Hibbing
French, Lyle A. ..... Minneapolis
Frethem, Allen A. ..... Rochester
Frey, Richard J. ..... Minneapolis
Friberg, Joseph B. ..... Minneapolis
† Fricke, Robert E. ..... Rochester
Fried, Louis A. ..... Minneapolis
† Friedell, Aaron ..... Minneapolis
Friedell, George ..... Minneapolis
Friedlieb, Oskar P. ..... Virginia
Friedman, Harry S. ..... Minneapolis
Friend, Charles A. ..... Minneapolis
† Fritsche, Albert ..... New Ulm
Fritsche, Carl J. ..... New Ulm
Fritsche, Theodore R. ..... New Ulm
Fritz, Wallace L. ..... St. Paul
Froats, Charles W. ..... St. Paul
Frost, John B. ..... Minneapolis
* Frost, Russell H. ..... Minneapolis
Fruchtman, Stanley A. ..... Minneapolis
Frye, Charles W. ..... St. Paul
Frykman, Howard M. ..... Minneapolis
Frys, Russell N. ..... Minneapolis
Fuglestad, Edson V. ..... Minneapolis
† Fuglestad, J. Roald ..... Brainerd

Fulks, Raymond W. ..... Minneapolis
Fuller, Alen M. ..... Lawton, OK
† Fuller, Alice H. ..... Minneapolis
Fuller, Benjamin F. ..... White Bear Lake
Fuller, Josiah ..... Duluth
† Fulton, Richard E. ..... Rochester
Funk, Victor K. ..... Hopkins
Funke, Joyce L. ..... St. Paul
Furlow, William L. ..... Rochester
Furman, L. Christine ..... Minneapolis
† Furman, Philip John ..... Rochester
Furr, Leo ..... Bird Island
Fusaro, Ramon M. ..... Minneapolis

G

Gaard, Richard C. ..... Robbinsdale
Gaebe, Milton B. ..... Clara City
Gaertner, Frank M. J., Jr. ..... St. Paul
Gaertner, John R. ..... St. Paul
Gaida, Joseph B. ..... St. Cloud
Gailitis, Veronika M. ..... St. Paul
Galbraith, Richard F. ..... Minneapolis
Galejs, Aina ..... Minneapolis
Gallett, Lester E. ..... Minneapolis
Galligan, John J. ..... St. Paul
† Galligan, Margaret Mary D. ..... Minneapolis
Galloway, Jackson R. ..... Alexandria, LA
Galway, Charles F. ..... Minneapolis
† Gambill, Carl M. ..... Rochester
Gambill, Earl E. ..... Rochester
† Gambill, Harold D. ..... San Jose, CA
† Gamble, Elbert J. ..... Roseville
Gamble, William G. ..... Minneapolis
Gamm, Edgar R. ..... Park Rapids
*† Gammell, John H. ..... Minneapolis
Garamella, Joseph J. ..... Minneapolis
Gannon, Paul G. ..... Minneapolis
Garber, George L. ..... Winona
Garber, James J. ..... Rochester
Gardner, Jack K. ..... Fairmont
† Gardner, Victor H. ..... Fairmont
Gardner, Walter P. ..... St. Paul
Garetz, Floyd K. ..... Minneapolis
Garrick, James G. ..... FPO San Francisco, CA
Garrow, Douglas M. ..... St. Paul
Garske, George L. ..... Minneaoplis
Garten, Joseph L. ..... Minneapolis
Garvey, James T. ..... Minneapolis
Gasior, Robert M. ..... APO San Francisco, CA
Gastineau, Clifford F. ..... Rochester
† Gau, Gerald T. ..... London, England
Gault, Neal L., Jr. ..... APO San Francisco, CA
Gaute, Svend T. ..... St. Paul
Gaviser, David ..... Minneapolis
Gedge, Stafford W. ..... Rochester
† Gehlen, Joseph N. ..... St. Paul
Geib, Marvin J. ..... Fargo, ND
Geiser, Peter M. ..... Alexandria
Geist, Robert W. ..... St. Paul
Geller, Joseph ..... Minneapolis
† Gentling, Peter A. ..... Rochester
George, Vane P., Jr. ..... Le Sueur
Geraci, Joseph E. ..... Rochester
Gerend, Thomas J. ..... Virginia
Gerstenkorn, George B. ..... Milaca
Gerster, Paul W. ..... Anoka
Geurs, Benjamin R. ..... Mankato
† Ghostley, Mary C. ..... Minneapolis
Gibbs, Edward C. ..... St. Paul
Gibbs, Robert W. ..... Minneapolis
Giebenhain, John N. ..... Minneapolis
Giere, Joseph C. ..... Minneapolis
Giere, Richard W. ..... Minneapolis
† Giere, Silas W. ..... Benson
† Giffin, Herbert Z. ..... Rochester
† Gilbaugh, James H., Jr. ..... Rochester
Gilbert, Maurice G. ..... Minneapolis
Gilbertsen, A. Sigrid ..... Minneapolis
Gilbertsen, Victor A. ..... Minneapolis
Gilchrist, Milton R. ..... St. Paul
Gildersleeve, Robert G. ..... Watertown
Gill, Theodore M. ..... Albert Lea
Gilles, Paul J. ..... Great Lakes, IL
Gillespie, Delmar R. ..... St. Paul
Gillespie, Malcolm G. ..... Duluth
Gillis, Samuel P. ..... Birmingham, AL
Gilman, Lloyd C. ..... Willmar
Gilsdorf, Donald A. ..... St. Paul
Gingold, Benjamin A. ..... Minneapolis
Gislason, Paul H. ..... Mankato
Gislason, Solveig T. ..... Edina
† Gisvold, John J. ..... APO San Francisco, CA
Gjerde, William P. ..... Lake City
Glaeser, John H. ..... Minneapolis
Gleason, Wallace A. ..... St. Paul
Glenny, William R. ..... St. Paul
Glick, Dallas D. ..... Mountain Lake
Glomstad, Gary B. ..... Deer River
† Gobel, Fredarick L. ..... Minneapolis
Goblirsch, Andrew P. ..... Sleepy Eye
Godfrey, H. Wilson ..... Minneapolis
Goehrs, Gilman H. ..... St. Cloud
Gokcen, Barbara W. ..... Minneapolis
Gokcen, Muharrem ..... Minneapolis
Gold, David ..... Minneapolis
Goldberg, Isadore M. ..... Minneapolis
Goldberg, Marvin E. ..... Minneapolis
Goldberg, Robert J. ..... St. Paul
Goldberg, Stanley M. ..... Minneapolis
Goldfarb, Benjie L. ..... Minneapolis
Goldfarb, Mace G. ..... Minneapolis
Goldish, Daniel R. ..... Duluth
Goldish, Robert J. ..... Duluth
† Goldman, Sherwin ..... Rochester
† Goldman, Theodore I. ..... Minneapolis
† Goldner, John C. ..... Rochester
Goldner, Meyer Z. ..... Minneapolis
Goldschmidt, Volker ..... Duluth
Goldsmith, Joseph W. ..... St. Paul
Goldstein, Alan L. ..... Hopkins
Goldstein, Norman P. ..... Rochester
Goldston, Edgar C. ..... Rochester
Gomez, Manuel R. ..... Rochester
Good, C. Allen, Jr. ..... Rochester
Good, Gary ..... Minneapolis
Good, Roy H. ..... Northfield
Goodchild, William R. ..... Minneapolis
Goodman, Ernest ..... St. Paul

Goodnow, William H. ..... Duluth
Goott, Bernard ..... St. Paul
Gordon, John R. ..... Minneapolis
† Gordon, Philip E. ..... Le Mesa, CA
Gordon, Sewell S. ..... Minneapolis
† Goren, Hershel ..... Rochester
Gorman, Columba A. ..... Rochester
Gould, Allan B., Jr. ..... Rochester
† Gould, Ronauld J. ..... Rochester
Govrik, Kalman ..... St. Paul
Gowan, Lawrence R. ..... Duluth
Gowan, Lawrence R., Jr. ..... Duluth
Gozum, Ekrem ..... Minneapolis
Gracey, Douglas R. ..... Belleville, IL
† Graf, John A. ..... Rochester
Graham, Asa B. ..... Faribault
Grahek, Jack P. ..... Ely
Grande, David W. ..... Mankato
Granquist, Richard D. ..... Minneapolis
Grant, John C. ..... Sauk Centre
Grant, Suzanne ..... Minneapolis
† Gratzek, Frank R. ..... Anoka
† Gray, Royal C. ..... Minneapolis
Green, Clayton R. ..... Excelsior
Green, Paul A. ..... Rochester
Green, Robert A. ..... St. Louis Park
Greenberg, Albert J. ..... Minneapolis
Greenberg, Eugene ..... Urbana, IL
† Greene, Gordon ..... Cherokee, IA
Greene, Jerry G. ..... St. Paul
Greene, Laurence F. ..... Rochester
Greene, Leonard H. ..... Minneapolis
Greenfield, Irving ..... Minneapolis
Greenfield, William T. ..... Cokato
Greenough, William G. ..... Dallas, TX
Greenwald, Stephen M. ..... Minneapolis
Gregg, James A. ..... Rochester
Gregoire, Earl ..... Bemidji
¶ Greisheimer, Esther M. .....Philadelphia, PA
Gretsch, Gerald A. ..... St. Paul
Gridley, John W. ..... Minneapolis
Griebie, Grant L. ..... Hutchinson
Griffin, John W. ..... Bemidji
Griffin, Patrick J. ..... Atlanta, GA
Griffin, Richard P. ..... Benson
Griffin, Thomas M. ..... St. Paul
Grimes, Allen E., Jr. ..... Coronado, CA
Grimes, Burton P. ..... St. Peter
Grimes, Marian ..... Minneapolis
Grimes, Paul T. ..... Park Rapids
Grimmell, Francis J. ..... Minneapolis
† Grindlay, John H. ..... Carbondale, CO
Grinvalds, Anna O. ..... Cambridge
Grismer, Jerome T. ..... Minneapolis
Grohs, William H. ..... Duluth
Gronquist, Y. K. J. ..... Cloquet
† Gronvall, Paul R. ..... Hopkins
Groover, Robert Vann ..... Rochester
Groschupf, Richard P. ..... Bemidji
† Groschupf, Theophilus P. ..... Bemidji
Grose, Frederick N. ..... Clarissa
Gross, John B. ..... Rochester
* Grotting, John K. ..... Minneapolis
Gruys, Robert I. ..... Minneapolis
Guerrero, Rafael A. ..... Minneapolis
Guilfoile, Pierre J. ..... Delano
Guillory, Joel R., Jr. ..... Lafayette, LA
Gulledge, Albert D. ..... Rochester
Gullickson, Glenn, Jr. ..... Minneapolis
Gumnit, Robert J. ..... St. Paul
Gunlaugson, Frederick G. ..... Minneapolis
Gustafson, Paul O. ..... Minneapolis
Gustafson, Robert W. ..... Granite Falls
Gustason, Harold T. ..... Minneapolis
Gustilo, Ramon B. ..... Minneapolis
Guthrie, J. Cameron ..... St. Paul
Guy, Jack A. ..... New London

H

Haas, Jack F. ..... Northfield
Haas, John W. ..... Minneapolis
Haavik, John E. ..... Duluth
† Habein, Harold C. ..... Palto Alto, CA
Haberer, Helen R. ..... Stacy
Haberle, Charles A. ..... Minneapolis
Haes, Julius E. ..... St. Peter
Haesly, Warren W. ..... Winona
Hagberg, Norman L. ..... Montevideo
Hagedorn, Albert B. ..... Rochester
Hagen, John D. ..... Austin
Hagen, Kristofer ..... Minneapolis
Hagen, Wayne S. ..... Minneapolis
Haglin, John J. ..... Minneapolis
Hahn, Richard G. ..... Rochester
† Haines, Samuel F. ..... Rochester
Hakanson, Erick Y. ..... St. Paul
Halbert, John J. ..... Duluth
Halenbeck, Philip L. ..... St. Cloud
Hall, Barnard ..... St. Paul
Hall, Harry B. ..... Minneapolis
Hall, Jack W. ..... Rochester
Hall, Wendell H. ..... Minneapolis
Hallberg, Olav Erik ..... Rochester
Hallenbeck, George A. ..... Rochester
Hallermann, Franz J. ..... Rochester
Hallgren, Roger B. ..... Belle Plaine
Halliday, Phillip V. ..... Duluth
Hallin, Roger P. ..... Minneapolis
† Halloran, Walter H. ..... Jackson
Halme, William B. ..... Wadena
Halper, Bernard ..... Hibbing
Halpern, Daniel ..... Minneapolis
Halpern, David J. ..... Brewster
Halpern, Joseph E. ..... Rush City
Halverson, Donald E. ..... Winnebago
Halverson, Kermit J. ..... Parkville
Halverson, William G. ..... Madelia
Halvorsen, Daniel K. ..... Owatonna
Halvorson, David C. ..... Northfield
Halvorson, James W. ..... Zumbrota
† Ham, Oscar E., Jr. ..... Rochester
Hambidge, Gove, Jr. ..... Minneapolis
Hamel, Arnold L. ..... Minneapolis
Hamel, Joseph I. ..... Minneapolis
Hammar, Lawrence M. ..... Mankato

Hamerstrom, Robert N. ..... Minneapolis
*† Hammes, Ernest M. ..... St. Paul
Hammes, Ernest M., Jr. ..... St. Paul
Handler, Seymour ..... Minneapolis
Hankerson, Robert G. ..... Mankato
Hanlon, David G. ..... Rochester
Hannah, Hewitt B. ..... Minneapolis
Hannon, Donald W. ..... St. Paul
Hanover, Ralph D. ..... International Falls
Hansen, Cyrus O. ..... Minneapolis
† Hansen, Erling W. ..... Hopkins
Hansen, Milo L. ..... Little Falls
† Hansen, Olga S. ..... Minneapolis
Hansen, Robert E. ..... Hibbing
Hansen, Rollin M. ..... Minneapolis
Hansen, Theodore M. ..... Albert Lea
Hanske, Edward A. ..... Minneapolis
Hanson, Bernard H. P. ..... Bigfork
Hanson, Ernest O. ..... Cloquet
Hanson, Everett C. ..... New York Mills
† Hanson, Harlow J. ..... Minneapolis
Hanson, Harold B. ..... Minneapolis
Hanson, Harold W. ..... Minneapolis
† Hanson, Henry V. ..... St. Paul
† Hanson, Jerome R. ..... Rochester
Hanson, Lewis ..... Frost
† Hanson, Malcolm B. ..... Osseo
Hanson, Mark C. L. ..... Minneapolis
Hanson, Mildred S. ..... Minneapolis
Hanson, Norbert O. ..... Rochester
† Hanson, William A. H. ..... Wayzata
Hanson, William B. ..... Minneapolis
Hanton, Edward M. ..... St. Paul
Harbaugh, John T. ..... St. Cloud
† Hardy, Kent M. ..... Rochester
Hargraves, Malcolm M. ..... Rochester
Harmon, Gaius E. ..... St. Paul
† Harrington, Donald P. ..... Richfield
† Harrington, Stuart W. ..... Rochester
Harrington, Vernon A. ..... Duluth
Harris, John E. ..... Minneapolis
Harris, Leon D. ..... Minneapolis
Harris, Lloyd E. ..... Rochester
Harris, Max E. ..... St. Paul
Harrison, Edgar G., Jr. ..... Rochester
Harrison, Percy W. ..... Worthington
Harrison, William C. ..... Minneapolis
Hart, William E. ..... Monticello
Hartfiel, William F. ..... St. Paul
Hartfield, James E., Jr. ..... Columbia, SC
Hartig, Marjorie ..... St. Paul
Hartig, Paul R. ..... Minneapolis
Hartjen, Jason K. ..... Bemidji
Hartman, Evelyn E. ..... Minneapolis
Hartnagel, Grant F. ..... Red Wing
Hartridge, Virginia B. ..... Rochester
Hartung, Elmer H. ..... Claremont
Hartwich, Roger F. ..... Winona
Hartwig, John A. ..... Minneapolis
† Harty, Jerome L. ..... Minneapolis
Hass, Frederick M. ..... Minneapolis
Hastings, Donald W. ..... Minneapolis
† Hastings, John D. ..... Rochester
† Hathaway, David S. ..... Arlington, VA
Haugan, Norman R. ..... Park Rapids
Hauge, Erling T. ..... Minneapolis
† Hauge, Malvin I. ..... Marcell
Haugen, George W. ..... Minneapolis
Haugen, John A. ..... Minneapolis
Hauser, Charles W. ..... St. Paul
Hauser, Donald C. ..... Minneapolis
† Hauser, George W. ..... Seattle, WA
† Hauser, Victor P. ..... St. Paul
Havel, Robert J. ..... Minneapolis
Haven, Walter K. ..... Minneapolis
*† Havens, John G. W. ..... Minneapolis
† Havig, Terrance A. ..... Rochester
Hawk, Dale J. ..... St. Charles
Hawkinson, Harlan W. ..... St. Paul
† Hawkinson, Raymond P. ..... Minneapolis
Hawley, George M. B., II ..... Red Wing
Hay, Lyle J. ..... Minneapolis
Hayes, Albert F. ..... St. Paul
Hayles, Alvin B. ..... Rochester
Hays, Albert T. ..... Minneapolis
Hays, James C. ..... APO New York, NY
Haywa, E. William ..... Minneapolis
Hazen, Richard W. ..... Willmar
Head, Douglas P. ..... Minneapolis
Hebbel, Robert ..... Minneapolis
† Hebeisen, Milton B. ..... Chaska
† Heck, Frank J. ..... Rochester
Heck, William W. ..... St. Paul
Hedemark, Homer H. ..... Ortonville
Hedemark, Truman A. ..... Ortonville
Hedenstrom, Charles W. ..... St. Paul
† Hedenstrom, Frank G. ..... St. Paul
Hedenstrom, Paul H. ..... Princeton
Hedenstrom, Philip C. ..... Marshall
Hedenstrom, Richard H. ..... St. Paul
Hedlund, Charles J. ..... St. Paul
Hedrick, William L. ..... Minneapolis
Heegaard, William G. ..... Alexandria
Hegrenes, Robert L. ..... Farmington
Hegstad, Thomas C. ..... Windom
Heiam, William C. ..... Cook
Heiberg, Olaf M. ..... Worthington
Heid, James K. ..... Little Falls
† Heidel, Werner ..... Cresskill, NJ
Heilig, William R. ..... St. Paul
Heimark, John J. ..... Mankato
Heinz, Ivy B. ..... Shakopee
Heinz, John N. ..... Minneapolis
Heinzerling, Carl R. ..... Chaska
Heise, Carl vR. ..... Winona
Heise, Herbert vR. ..... Winona
Heise, Paul vR. ..... Winona
Heise, Philip vR. ..... Winona
Heise, William vR. ..... Winona
Heisel, John G. ..... Duluth
Held, Wm. J. ..... St. Cloud
Heller, Edgar E. ..... Mankato
Helseth, Hovald K. ..... Fergus Falls
Helwig, Karl L. ..... Virginia
Henderson, Darrell L. ..... Portsmouth, VA
Henderson, Edward D. ..... Rochester
Henderson, John W. ..... Rochester
Henderson, Lowell L. ..... Rochester
† Henderson, R. Michael ..... Rochester
Henderson, Terrance P. ..... White Bear Lake
† Hengstler, William H. ..... St. Paul
Henke, Wilbert J. ..... St. Paul
Henrikson, Earl C. ..... Minneapolis
† Henry, Clarence J. ..... Onamia
Henry, Harold W. ..... Moose Lake
Henry, James S. ..... St. Paul
Henry, John C. ..... Owatonna
Henry, Joseph E. ..... Milaca

Henry, Kenneth G. ..... Owatonna
Hepper, Norman G. ..... Rochester
Herber, Leo ..... Thief River Falls
Herbert, Willis L. ..... Minneapolis
Herman, Samuel M. ..... St. Paul
Hermans, Paul E. ..... Rochester
Herrick, Donald W. ..... St. Paul
† Hertel, Garfield E. ..... McAllen, TX
† Hertzler, Jerrad J. ..... Rochester
Hesla, Inman A. ..... Austin
Hess, Carroll N. ..... Minneapolis
† Hetzler, John A. ..... White Bear Lake
† Hewitt, Edith S. ..... Clearwater Beach, FL
Hewitt, Marshall I. ..... Minneapolis
† Hewitt, Richard M. ..... Clearwater Beach, FL
Hiatt, John A. ..... Minneapolis
Hickok, David F. ..... Minneapolis
Higdon, Donald A. ..... St. Cloud
Higgins, John A. ..... Rochester
Higgs, Paul C. ..... Virginia
Hildebrand, John E. ..... Bemidji
† Hildebrandt, Walter C. ..... Minneapolis
Hilding, Anderson C. ..... Duluth
Hilgedick, William R. ..... St. Paul
Hilger, Jerome A. ..... St. Paul
Hilger, John R. ..... St. Paul
Hilger, Laurence D. ..... St. Paul
Hilgermann, George O. ..... Minneapolis
Hilgers, Robert D. ..... Great Lakes, IL
Hilker, Marcus D. ..... St. Paul
Hilker, Robert T. ..... Owatonna
Hill, Charlotte W. ..... St. Paul
Hill, Earl ..... Minneapolis
Hill, Elmer M. ..... Minneapolis
Hill, John R. ..... Rochester
Hill, Richard W. ..... Rochester
Hiller, Bruce H. ..... Minneapolis
Hinckley, Robert G. ..... White Bear Lake
Hinderaker, Harris P. ..... Willmar
Hines, Edgar A., Jr. ..... Brevard, NC
Hiniker, Louis P. ..... St. Paul
Hiniker, Peter J. ..... St. Peter
Hinz, Walter E. ..... Willmar
† Hirschboeck, Frank J. ..... Duluth
Hirsh, Stanton A. ..... Crookston
Hitchcock, Claude R. ..... Minneapolis
Ho, Shu Kang ..... St. Paul
† Hoagland, H. Clark ..... San Antonio, TX
Hodapp, Robert V. ..... Willmar
Hodges, Kenneth V. ..... Minneapolis
Hodgson, Corrin H. ..... St. Paul
Hodgson, Jane E. ..... St. Paul
Hodgson, John R. ..... Rochester
Hoeg, Dwight C. ..... Duluth
† Hoehn, James G. ..... Rochester
Hoeper, Philip G. ..... Mankato
Hoff, Herbert O. ..... Duluth
Hoffert, Henry E. ..... Minneapolis
Hoffman, David L. ..... Rochester
Hoffman, Roy A. ..... Minneapolis
Hoffman, Walter Lees ..... Minneapolis
Hofmann, Gerald N. ..... Minneapolis
Hoganson, Donald E. ..... Bemidji
Hohmann, Albert ..... St. Paul
*† Hoidale, Andrew D. ..... Tracy
Holbrook, Margaret A. ..... Rochester
† Holcomb, Joel T. ..... Marine-on-St. Croix
† Holcomb, O. William ..... St. Paul
Holland, C. R. ..... Rochester
Hollenhorst, Robert W. ..... Rochester
Holley, Keith E. ..... Rochester
Hollinshead, W. H. ..... St. Paul
Holm, Owen W. ..... Crookston
Holman, Colin B. ..... Rochester
Holmberg, Conrad J. ..... Minneapolis
*† Holmberg, LeRoy J. ..... Canby
Holmstrom, Carle H. ..... Warren
Holt, Glen E. ..... Duluth
Holt, John E. ..... St. Paul
Holten, David R. ..... Minneapolis
Holten, John ..... Moorhead
Holzapfel, Fred C. ..... Minneapolis
Hom, Leong Y. W. ..... Fergus Falls
Honath, Donald H. ..... Owatonna
† Hood, Roderick P. ..... Rochester
Hoover, Norman W. ..... Rochester
Hopkins, G. Wendell ..... Minneapolis
Hopperstad, J. Jerome ..... Minneapolis
Hoppes, Emerson E. ..... Minneapolis
Horns, Howard L. ..... Minneapolis
Horns, Norman ..... Minneapolis
Horns, Richard C. ..... Minneapolis
† Horton, Bayard T. ..... Rochester
Hoseth, Wayne L. ..... Minneapolis
Hottinger, George C. ..... St. Paul
Hottinger, Raymond C. ..... Janesville
Houglum, Arvid J. ..... Duluth
† Houkom, Bjarne ..... Hamilton, MT
Houkom, S. Sverre ..... Duluth
† Houle, Rollin J. ..... New Brighton
Houlton, William H. ..... St. Paul
Hourigan, Thomas S. ..... Minneapolis
Houts, Joseph C. ..... Dassel
Hovde, Gordon W. ..... Lindstrom
Hovland, Melvin L. ..... Minneapolis
Hovland, Richard D. ..... Minneapolis
Howard, Frank M., Jr. ..... Rochester
Howard, Robert B. ..... Minneapolis
Howard, Solomon E. ..... Minneapolis
Howe, Newell W. ..... West St. Paul
Howell, Carter W. ..... Minneapolis
† Howell, John L. ..... Rochester
Howell, Llewelyn P. ..... Rochester
Hoyer, Ludolf J. ..... Windom
Hoyt, C. Sherman ..... Minneapolis
Hruza, William J. ..... Madelia
Huber, Robert W. ..... St. Croix Falls, WI
Hubin, Edwin G. ..... Sandstone
Hudgins, Robert L. ..... Ft. Benning, GA
† Hudson, George E. ..... Minneapolis
Huebert, Dan W. ..... Hutchinson
† Huenekens, Edgar J. ..... Minneapolis
Huff, John S. ..... Minneapolis
Huffington, Herb L. ..... Waterville
† Huffington, Herbert L. ..... Lutsen
Hughes, Bernard J. ..... St. Cloud
Hughes, Sidney O. ..... Winona
Huizenga, Kenneth A. ..... Rochester
Hulteng, Donald B. ..... Minneapolis
† Hultkrans, Rudolph E. ..... Minneapolis
† Hummer, William K. ..... Rochester
Hunder, Gene G. ..... Rochester
† Hunt, Arthur B. ..... Carmel, CA
Hunt, James C. ..... Rochester
Hunt, Vincent R. ..... Red Lake Falls
Hunter, Murray H. ..... Farmington
Hunter, Samuel W. ..... St. Paul

Hurr, Maland C. ..... Minneapolis
Hurwitz, Milton M. ..... St. Paul
Huseby, Thomas L. ..... St. Paul
Husebye, Kjeld O. ..... St. Paul
Hustad, Edward G. ..... Minneapolis
Hutchinson, Henry ..... St. Cloud
Hymes, Charles ..... Minneapolis

I

Ibrahim, George W. ..... Virginia
*† Ide, Arthur W. ..... St. Paul
Ide, Arthur W., Jr. ..... Minneapolis
Idstrom, Linneus G. ..... Minneapolis
Indeck, Walter ..... Minneapolis
Ingalls, Edgar G. ..... Minneapolis
† Ireland, Gerald W. ..... St. Paul
† Irwin, Jack C., Jr. ..... Rochester
† Isbell, Robert G. ..... Rochester
Isele, Reginald H. ..... Austin
Iverslie, Philip C. ..... Minneapolis
Iverson, Eleanor B. ..... Minneapolis
Iverson, Rolf M. ..... Minneapolis
Ivins, John C. ..... Rochester

J

Jackish, George E. ..... Red Wing
Jacklin, Alexander J. ..... Duluth
Jackman, Raymond J. ..... Rochester
Jackson, J. Albert ..... Minneapolis
Jackson, Richard L. ..... Minneapolis
Jackson, William C. ..... St. Paul
Jacobs, Douglas L. ..... Willmar
Jacobson, Clarence ..... Chisholm
Jacobson, Clifford W. ..... Breckenridge
Jacobson, Ferdinand C. ..... Duluth
Jacobson, Leslie W. ..... Minneapolis
Jacobson, Loren J. ..... Minneapolis
† Jacobson, Stephen G. ..... Rochester
Jacobson, Wyman E. ..... Minneapolis
Jackott, William E. ..... Duluth
Jaeger, Dwight E. ..... St. Cloud
Jaffe, Manuel O. ..... Minneapolis
James, Ellery M. ..... St. Paul
James, John W. ..... St. Paul
Janda, George W., Jr. ..... Minneapolis
† Janda, Wayne E. ..... Rochester
Janecek, James, Jr. ..... New Brighton
Janecky, Allen G. ..... Baudette
† Janes, Donald R. ..... Rochester
Janes, Joseph M. ..... Wausau, WI
Janssen, Martin E. ..... St. Paul
Jarvis, Charles W. ..... St. Paul
Jastram, Rupert M. ..... St. Paul
Jay, Alan R. ..... Rochester
Jefferies, William L. ..... St. Louis Park
Jensen, Alvin M. ..... Brownton
Jensen, John ..... Crookston
Jensen, Nathan K. ..... Minneapolis
Jensen, Paul A. ..... Minneapolis
Jensen, Reynold A. ..... Minnetonka
† Jensen, Thorvold J. ..... Duluth
Jenson, James E. ..... Stillwater
Jepson, William W. ..... Minneapolis
† Jereb, John A. ..... Rochester
Jerome, Bourne ..... Minneapolis
Jerome, Elizabeth B. K. ..... Minneapolis
Jeronimus, Henry J. ..... Duluth
Jessico, Charles M. ..... Duluth
Jeub, Robert P. ..... Minneapolis
Jinkins, Roger E. ..... Minneapolis
Johanson, Waldemar G. ..... St. Paul
† Johanson, Waldemar G., Jr. ..... Dallas, TX
John, Byron L. ..... St. Cloud
Johnson, Alan R. ..... Windom
Johnson, Aldridge F. ..... St. Paul
Johnson, Angelo G. ..... Minneapolis
Johnson, Arthur B. ..... Minneapolis
Johnson, Bradley D. ..... Minneapolis
Johnson, Calvin J. ..... Grand Rapids
Johnson, Carl Edwin ..... St. Paul
Johnson, Carl Eric ..... Rochester
Johnson, Carolyn A. ..... St. Paul
Johnson, C. Percy ..... Tyler
Johnson, Curtis A. ..... Olivia
Johnson, Curtis M. ..... Winona
Johnson, Daniel A. ..... Litchfield
† Johnson, David C. ..... Rochester
Johnson, David R. ..... Minneapolis
Johnson, Dexter W. ..... Great Falls, MT
Johnson, Donald A. ..... Minneapolis
Johnson, Douglas L. ..... Little Falls
Johnson, Edward A. ..... Minneapolis
† Johnson, Einer W. ..... Bemidji
Johnson, Einer, W., Jr. ..... Rochester
Johnson, Frank E. ..... Minneapolis
Johnson, Franklin L. ..... Duluth
Johnson, Gerhard J. ..... Portsmouth, VA
Johnson, Gordon E. ..... Minneapolis
Johnson, Harry A., Jr. ..... Minneapolis
Johnson, Herbert W. ..... St. Paul
† Johnson, James A. ..... Minneapolis
Johnson, John W. ..... Minneapolis
Johnson, Karl E. ..... Duluth
† Johnson, Kenneth A. ..... Rochester
Johnson, L. Morris ..... Washington, DC
Johnson, Marvin W. ..... Dassel
Johnson, Norman P. ..... Minneapolis
Johnson, Norman Paul ..... St. Paul
Johnson, Norton T. ..... Minneapolis
Johnson, O. Guy ..... Bayport
Johnson, Olga H. ..... Moorhead
Johnson, Ralph B. ..... Lanesboro
Johnson, Reinald G. ..... Minneapolis
† Johnson, Reuben A. ..... Minneapolis
Johnson, Rex R. ..... New Ulm
Johnson, Richard J. ..... St. Paul
Johnson, Richard S. ..... Minneapolis
Johnson, Robert E. ..... Minneapolis
Johnson, Robert H. ..... St. Paul

Johnson, Theodore ..... Duluth
Johnson, Thomas E. ..... St. Paul
Johnson, Thomas H., Jr. ..... Minneapolis
Johnson, Vilhelm M. ..... Dawson
Johnson, William E. ..... St. Cloud
Johnson, William J. ..... Rochester
Johnson, Youbert T. ..... Minneapolis
Johnsrud, Luverne W. ..... Hibbing
Johnston, Bemis H. ..... Eatontown, NJ
Johnston, Donald K. ..... Minneapolis
Johnston, H. Wayne ..... Virginia
Johnston, Leonard F. ..... Winona
Jones, David G. ..... Minneapolis
Jones, H. Royden, Jr. ..... APO New York, NY
† Jones, Harry F. ..... Rochester
† Jones, Herbert W., Jr. ..... Minneapolis
Jones, Orville H. ..... Mankato
Jones, Richard H. ..... Minneapolis
† Jones, Richard N. ..... St. Cloud
Jordan, Donald V. ..... Minneapolis
† Jordan, Kathleen B. Smith ..... Granite Falls
† Jordon, James J. ..... Rochester
† Jorgensen, Edward O. ..... Fergus Falls
Jorgensen, Donald R. ..... St. Paul
Jorgensen, Harlan ..... Minneapolis
Joseph, Arnold H. ..... St. Paul
† Joy, Wm. B. ..... Rochester
Joyce, John W. ..... Rochester
Judd, Allen S. ..... Minneapolis
Judd, Edward S. ..... Rochester
Judd, Walter H. ..... Washington, DC
† Juergens, Herman M. ..... Belle Plaine
Juergens, John L. ..... Rochester
Juergens, Manley F. ..... Stillwater
Juers, Edward H. ..... Red Wing
Juntunen, Roy R. ..... Duluth
Jurdy, Mitchell ..... Minneapolis
Just, Herman J. ..... Hastings

K

Kadesky, Harold B. ..... Minneapolis
Kaese, Werner E. ..... Rochester
Kaiser, Harold B. ..... Minneapolis
Kaiser, Milton L. ..... New Ulm
Kalb, Thomas J. ..... Minneapolis
Kallestad, Leonard L. ..... Wayzata
Kane, Dennis J. ..... Minneapolis
Kane, Morton C. ..... Minneapolis
Kane, William J. ..... Minneapolis
Kanne, Earl R. ..... Brainerd
Kaplan, David H. ..... Minneapolis
Kaplan, Harold A. ..... Minneapolis
Kaplan, J. Jacob ..... Minneapolis
Kapsner, Adrian L. ..... Minneapolis
* Kapsner, Alfred T. ..... Princeton
Karabeyoglu, Turgut ..... Hastings
Karges, Laurel E. ..... Grand Rapids
Karish, Louis J. ..... Grand Rapids
Karleen, Conrad I. ..... Minneapolis
Karlen, Markle ..... Minneapolis
Karn, Jacob F. ..... Ortonville
Karnes, William E. ..... Rochester
Karon, Everett H. ..... St. Paul
Karon, Irvine M. ..... St. Paul
Karrow, John W. ..... Granite Falls
† Kasher, R. Jerome ..... Rochester
Kasper, Eugene M. ..... St. Paul
Kasper, Robert E. ..... Excelsior
Kath, Reinhard H. ..... Arlington
Katkov, Harold ..... Wayzata
Katz, Beni ..... Minneapolis
Katz, Elliott S. ..... Rochester
Katz, Louis J. ..... Long Beach, CA
Kaufman, Edward J. ..... Appleton
† Kaufman, William C. ..... Appleton
Kavanaugh, Gerald J. ..... Rochester
Kazmier, Francis J. ..... Ft. Leavenworth, KS
Kearney, R. Wynn ..... Mankato
Kearns, Thomas P. ..... Rochester
Keating, F. Raymond ..... Rochester
Keil, Marcus A. ..... Albert Lea
Keith, Haddow M. ..... Rochester
† Keith, Norman M. ..... Rochester
Keith, Paul J. ..... Milaca
Keithahn, Elmer E. ..... Sleepy Eye
Kelalis, Panayotis P. ..... Rochester
† Kelby, Gjert M. ..... Minneapolis
Kelley, Roger E. ..... Crosby
Kelly, Albert C. ..... St. Paul
Kelly, Charles F. ..... Minneapolis
Kelly, Edward H. ..... St. Paul
Kelly, Helen M. ..... St. Paul
Kelly, James H. ..... St. Cloud
Kelly, John C. ..... Minneapolis
Kelly, John F. ..... Cold Spring
Kelly, John P. ..... Minneapolis
Kelly, John T. ..... Minneapolis
Kelly, Joseph R. ..... St. Paul
Kelly, Patrick, J. ..... Rochester
Kelly, Robert T. ..... Grand Rapids
† Kelsey, Carleton G. ..... St. Paul
Kelsey, Chauncey M. ..... St. Paul
† Kemp, Alphonse F. ..... Mankato
Kempers, Roger D. ..... Rochester
Kenefick, Emmett V. ..... St. Paul
† Kenefick, Thomas P. ..... Los Angeles, CA
Kennedy, Byrl J. ..... Minneapolis
Kennedy, Charles C. ..... Rochester
† Kennedy, Claude C. ..... Minneapolis
† Kennedy, George L. ..... Faribault
Kennedy, William R. ..... Minneapolis
Kenyon, Thomas J. ..... St. Paul
† Kern, Eugene B. ..... Rochester
† Kernohan, James W. ..... Rochester
Kerr, Frederick W. L. ..... Rochester
† Kesting, Herman ..... St. Paul
Kevern, Jay L. ..... Henning
Keyes. Robert W. ..... Pipestone
Keys, Thomas F. ..... FPO San Francisco, CA
Khorsand, Darius ..... Minneapolis
† Kieffer, Stephen A. ..... Minneapolis
Kiely, Joseph M. ..... Rochester
Kierland, Robert R. ..... Rochester
Kiesler, Frank ..... Grand Rapids
Kilbride, Edwin A. ..... Worthington
Kilen, Mark J. ..... Ft. Lewis, WA
Kim, Mark K. ..... Minneapolis
Kimmel, George C. ..... Minneapolis
Kincaid, O. W. ..... Rochester
King, Frances W. ..... Minnetonka

† King, John E. ..... Rochester
Kinkade, Byron R. ..... Ada
Kinney, William N. ..... St. Paul
† Kinsella, Thomas J. ..... Minneapolis
Kiolbasa, Edward B. ..... Stillwater
Kippen, Neil ..... Breckenridge
Kirby, Thomas J., Jr. ..... Rochester
Kirklin, John W. ..... Birmingham, AL
Kiser, Joseph C. ..... Minneapolis
Kitchen, Clyde K. ..... Minneapolis
Kitzberger, Peter J. ..... New Ulm
Kjellsen, Douglas L. ..... Minneapolis
Klass, Donald W. ..... Rochester
Klassen, Arthur C. ..... Minneapolis
Klefstad, Lloyd H. ..... Greenbush
† Klein, Harry ..... Duluth
*† Klein, William A. ..... Duluth
Kleinsasser, Warren L. ..... Farmington
Kleven, Lowell H. ..... Minneapolis
Kline, Richard J. ..... Grand Forks, ND
Knapp, James F. ..... Detroit Lakes
Knapp, Miland E. ..... Minneapolis
Knapp, Robert D., Jr. ..... Rochester
† Knight, Ralph T. ..... Minneapolis
† Knight, Ray R. ..... Minneapolis
Knip, Robert J. ..... Ortonville
Knipp, William J. ..... Brainerd
Knobloch, William H. ..... Minneapolis
Knoche, Harvey A. ..... Gaylord
Knoedler, John P. ..... Duluth
Knoll, W. V. ..... Brainerd
Knowles, Richard A. ..... Coon Rapids
Knudsen, Helen L. ..... Minneapolis
Knutson, Gerhard E. ..... St. Paul
Knutson, Lewis A. ..... Spring Grove
Knutson, Robert C. ..... St. Paul
Kodres, Nina ..... St. Paul
Koelsche, Giles A. ..... Rochester
Koenig, Robert P. ..... St. Cloud
*† Kohlbry, Carl O. ..... Duluth
Kohlhase, Robert E. ..... Minneapolis
Kolars, Charles P. ..... Minneapolis
Kolars, James J. ..... Faribault
† Kolb, Marvin O. ..... Rochester
† Koller, Hermann M. ..... Minneapolis
† Koller, Louis R. ..... Minneapolis
Koller, Robert L. ..... Minneapolis
† Kollmorgen, Rodger C. ..... Minneapolis
Kooda, Jennings C. ..... Morris
Koons, William R. ..... Mahnomen
Koontz, Peter S. ..... Minneapolis
Koop, Severin H., Jr. ..... St. Cloud
Koos, Gerald W. ..... Minneapolis
Korchik, John P. ..... Minneapolis
Korda, Henry A. ..... Pelican Rapids
Koropchak, Nikolai ..... Minneapolis
Kosiak, Michael ..... St. Paul
Kosiak, William ..... Two Harbors
Koskela, L. E. ..... St. Peter
Kostich, Nikola D. ..... Minneapolis
Kostick, William R. ..... Fertile
Kotchevar, Frank R. ..... Minneapolis
Kottke, Bruce A. ..... Rochester
Kottke, Frederic J. ..... Minneapolis
Kotval, Russell J. ..... Pipestone
Koucky, Rudolph W. ..... Minneapolis
Kovack, Freeman D. ..... Minneapolis
Koza, Donald W. ..... St. Paul
Kozak, Michael J. ..... Minneapolis
Kozel, William J. ..... Morris
Kraatz, Robert W. ..... St. Paul
Kraemer, George N. ..... Fairmont
Krafft, Walter E. ..... Minneapolis
Kragh, Lyle V. ..... Minneapolis
† Kramer, Daniel W. ..... Minneapolis
Kramer, James D. ..... St. Paul
Krause, Carl W. ..... Fairmont
Kremen, Arnold J. ..... Minneapolis
Kremer, Jerome L. ..... Montevideo
† Kreuzer, Titus C. ..... Ft. Snelling
Krezowski, Thomas K. ..... St. Paul
Krieser, Albert E. ..... Minneapolis
† Krigsten, Eli J. ..... Rochester
Krueger, Victor R. ..... Nopeming
Krupp, Neal E. ..... Rochester
Kruzich, Stephen J. ..... St. Cloud
Krystosek, Lee A. ..... Minneapolis
† Kubista, Theodore P. ..... Rochester
† Kucera, Frank J. ..... Hopkins
† Kucera, Stanley T. ..... Northfield
† Kucera, William J. ..... Santa Barbara, CA
Kugler, Alex A. ..... St. Paul
Kuhlmann, Lawrence B. ..... Melrose
Kuhlmann, Vernon G. ..... Alexandria
† Kullmann, George L. ..... Rochester
Kulstad, Oscar S. ..... Dodge Center
Kulzer, Norbert J. ..... Hastings
Kump, Warren L. ..... Minneapolis
Kundel, Donald W. ..... Duluth
Kuske, Albert W. ..... St. Paul
Kusske, Bradley W. ..... St. Paul
Kusske, Douglas R. ..... St. Paul
Kusz, Clarence V. ..... Minneapolis
Kuz, Eugene L. ..... Savage
Kvale, James N. ..... Atwater
Kvale, Walter F. ..... Rochester
† Kvam, Lowell L. ..... St. Paul
Kvistberg, Gerald K. ..... St. Cloud
Kyle, Robert A. ..... Rochester
Kyllo, John E. ..... Minneapolis

L

L'Abbe, A. J. Philip ..... Duluth
La Brec, H. C. ..... Mankato
LaBree, John W. ..... Minneapolis
LaBree, Robert H. ..... Duluth
Lade, Roswith I. ..... St. Paul
LaFave, James W. ..... St. Paul
LaFond, Edward M. ..... St. Cloud
Lagaard, Sheldon ..... Minneapolis
LaHood, Joseph J. ..... Long Beach, CA
Laikola, Leslie A. ..... Adrian
† Lajoie, John M. ..... Minneapolis
Lake, Clifford F. ..... Rochester
LaLonde, John B. ..... Bemidji
Lamb, H. Douglas ..... Minneapolis
Lampert, Ronald M. ..... St. Paul
Lane, Miles I. ..... White Bear Lake
Lang, Leonard A. ..... Minneapolis
Langer, Leonard O., Jr. ..... Minneapolis
Langseth, Rodney N. ..... Duluth

Lannin, Bernard G. ..... St. Paul
Lannin, Donald R. ..... St. Paul
Lannon, James B. ..... Minneapolis
† Lapierre, Arthur P. ..... Minneapolis
Lapp, N. LeRoy ..... Morgantown, WV
Larkin, John E. ..... St. Paul
† Laroche, Gilles ..... Rochester
Larrabee, Walter F., Jr. ..... Willmar
Larsen, Frank W. ..... Minneapolis
Larsen, Russell H. ..... Lakefield
Larson, Arthur K. ..... Minneapolis
Larson, Donald Marvin ..... Minneapolis
Larson, Donald Myren ..... Duluth
Larson, Dorette W. ..... Fergus Falls
Larson, Ernest J., Jr. ..... Minneapolis
Larson, Eva Jane O. ..... St. Paul
Larson, F. Wilmer ..... Minneapolis
Larson, Gerald E. ..... Cambridge
Larson, Keith D. ..... Moose Lake
Larson, Kenneth R. ..... Moose Lake
Larson, Lawrence M. ..... Minneapolis
Larson, Leighton W. ..... Waconia
† Larson, Leonard M. ..... Minneapolis
Larson, Leroy J. ..... Bagley
Larson, Loren J. ..... Minneapolis
Larson, Milo H. ..... St. Peter
Larson, Oliver E. H. ..... Zumbrota
Larson, Paul N. ..... Minneapolis
Larson, Richard E. ..... Minneapolis
† Larson, Richard H. ..... Rochester
Larson, Roger C. ..... Minneapolis
† Larson, Stephen L. ..... Rochester
Larson, Wyllis G. ..... Minneapolis
Laszewski, Franz von Zelberschwecht ..... St. Paul
Latterell, Kenneth E. ..... Duluth
† Lattin, John E., III ..... Rochester
Latts, Elliot M. ..... Minneapolis
† Laurnen, Edwin L. ..... Rochester
† Lavertu, Julien G. ..... Rochester
† LaVake, Rae T. ..... Minneapolis
Law, Harrison E. ..... Virginia
Lawler, Kevin M. ..... St. Paul
† Lawrence, Henry M., Jr. ..... Lookout Mt., TN
Lawrence, Van S. ..... Rochester
Lawrow, John W. ..... Minneapolis
Lawson, Warren R. ..... Minneapolis
Lawton, James J., Jr. ..... Minneapolis
Laymon, Carl W. ..... Minneapolis
Layton, Donald D. ..... Rochester
† Leach, Clifford G. ..... Minneapolis
Leach, Thomas C. ..... Babbitt
† Leavelle, Dennis E. ..... Rochester
Leavenworth, Richard O., Jr. ..... Minneapolis
† Leck, Paul C. ..... Palm Desert, CA
Lee, Gordon E. ..... Glenwood
Lee, Hubert W. ..... Brainerd
Lee, Norman J. ..... Tracy
Lee, Raymond A. ..... Rochester
Lee, Robert E. ..... Rochester
Lee, William C. ..... Hibbing
Leek, Joseph H. ..... Duluth
Leemhuis, Andrew J. ..... Minneapolis
Lees, David C. ..... Minneapolis
Lees, Jack R. ..... St. Paul
Lehman, Donald S. ..... St. Paul
Lehrer, Alfred J., Jr. ..... Montgomery
Leick, Richard M. ..... St. Paul
Leiferman, Robert J. ..... Minneapolis
Leighton, John S. ..... Patuxent River, MD
Leinonen, Wendla E. ..... Anoka
† Leitch, Archibald ..... St. Paul
Leitch, Cecil M. ..... Litchfield
Lelwica, Thaddeus J. ..... Staples
Lenander, Mellvin E. L. ..... St. Peter
Lenarz, Albert J. ..... St. Cloud
Lende, Norman ..... Faribault
Lenz, Bernard W. ..... Minneapolis
Lenz, Joseph R. ..... Morton
Lenz, Oa ..... Minneapolis
† Leonard, Lawrence J. ..... Minneapolis
Leonard, Paul F. ..... Rochester
Leonard, Samuel ..... Minneapolis
Leonard, Stanley A. ..... St. Paul
Leonardson, Peter Y. ..... Red Lake Falls
† Leopard, Brand A. ..... Brownsville, TX
† Lepak, Francis J. ..... Duluth
† Lepak, John A. ..... St. Paul
Leppink, Harold B. ..... Two Harbors
Leppo, N. Erkki A. ..... Duluth
Lerdahl, Kenneth ..... St. Paul
Lerner, A. Ross ..... Minneapolis
Leslie, Loren R. ..... Minneapolis
Leslie, W. Robert ..... Minneapolis
Lessard, Richard J. ..... St. Paul
Lester, John W. ..... Mapleton
Lester, Malcolm J., Jr. ..... Truman
Lester, Theodore H. ..... Minneapolis
Leston, Robert D. ..... Minneapolis
Leven, N. Logan ..... St. Paul
Leverenz, Carleton W. ..... St. Paul
Levine, Howard M. ..... Minneapolis
† Levitan, Alxander A. ..... Minneapolis
Levitan, Leonard H. ..... St. Paul
Levitt, George X. ..... St. Paul
Lewis, Andrew J. ..... Rochester
Lewis, Charles W. ..... Henning
Lewis, F. Bruce ..... Minneapolis
Lewis, Glenn M., Jr. ..... Minneapolis
Lewis, Joyce S., Jr. ..... Minneapolis
Lick, Charles L. ..... St. Paul
Lick, Louis C. ..... Minneapolis
Lick, William J. ..... St. Paul
Liebhaber, Henia F. ..... Anoka
Lein, Richard J. ..... St. Paul
† Liffrig, William W. ..... Red Wing
† Lightbourn, Edgar L. ..... Hastings
Lilleberg, Norbert J. ..... St. Paul
Lillehei, Richard C. ..... Minneapolis
Lillie, Andrew R. ..... St. Paul
Lillie, John C. ..... Rochester
Lima, Ludvig R. ..... Montevideo
Limbeck, Donald A. ..... Robbinsdale
Lindahl, Merlyn J. ..... Sherburn
† Lindall, Arnold W., Jr. ..... Minneapolis
Lindberg, Vernon L. ..... Minneapolis
Lindberg, Winston R. ..... Minneapolis
Lindblom, Alton E. ..... North Mankato
Lindblom, Maurice L. ..... Minneapolis
Lindeland, Arthur T. ..... Dublin, CA
Lindell, Robert E. ..... St. Paul
Lindeman, Raymond J. ..... Paynesville
Lindemann, Charles E. ..... Minneapolis
Linderholm, Bruce E. ..... Minneapolis
Lindgren, Russell C. ..... Minneapolis
Lindley, Stanley B. ..... St. Cloud
Lindquist, Dale C. ..... Lindstrom
Lindquist, Max F. ..... South St. Paul

† Lindquist, Richard H. ..... Minneapolis
Lindsay, Malcolm I., Jr. ..... Rochester
Lindseth, Esten O. ..... Minneapolis
Linke, Charles A. ..... Duluth
Linke, Clara L. ..... Duluth
Linman, James W. ..... Rochester
Linnell, Leonard S. ..... Owatonna
Linner, John H. ..... Minneapolis
† Linner, Paul W. ..... Minneapolis
Linscheid, Ronald L. ..... Rochester
Lippman, Hyman S. ..... St. Paul
Lippmann, Elmer W. ..... Hutchinson
Lipschultz, Oscar ..... St. Louis Park
Lipscomb, Paul R. ..... Rochester
Litin, Edward M. ..... Rochester
Litkewitsch, Helene ..... St. Paul
Litman, Abraham B. ..... Minneapolis
† Litman, Samuel N. ..... Duluth
† Litman, Thomas ..... St. Louis Park
Litzow, Thaddeus J. ..... Rochester
† Lloyd, Judson F. ..... APO, San Francisco, CA
Lober, Paul H. ..... Minneapolis
Locke, Murray S. ..... Minneapolis
Loeb, George ..... St. Cloud
Loes, Louis A. ..... St. Cloud
Lofgren, Eric P. ..... Rochester
Lofgren, Karl A. ..... Rochester
Lofsness, Stanley V. ..... Minneapolis
Lofstrom, Dennis E. ..... Brainerd
Logan, George B. ..... Rochester
Logothetis, John A. ..... Minneapolis
Lohmann, John G. ..... Pipestone
Loken, Merle K. ..... Minneapolis
Loken, Selmer M. ..... St. Paul
Loken, Theodore ..... Ada
† Lommen, Peter A. ..... Austin
Lommen, Peter A., Jr. ..... Austin
Longfellow, Helen W. ..... Brainerd
† Long, Richard J. ..... Quebec, Canada
† Longo, Margaret F. ..... Lafayette, LA
Loomis, George L. ..... Winona
Lorentzen, Ernest S. ..... Detroit Lakes
Lott, Frederick H. ..... Minneapolis
† Love, Frederick A. ..... Carlos
Love, J. Grafton ..... Rochester
† Lovett, Beatrice R. ..... Minnetonka
Lowe, Alexander D. ..... South St. Paul
Lowe, Douglass A. ..... Minneapolis
† Lowe, Thomas A. ..... South St. Paul
Lowry, Elizabeth C. ..... Minneapolis
Lowry, Jeanette K. ..... Minneapolis
Lowry, Paul T. ..... Minneapolis
Lowry, Thomas ..... Minneapolis
Lu, Cheng-en ..... Fergus Falls
Luby, Thomas H. ..... St. Cloud
† Luck, Hilda ..... Mankato
† Ludes, Bernard F. ..... Rochester
Lueck, Wallace W. ..... Minneapolis
Lueders, James ..... Evansville
Lufkin, Murray W. ..... St. Paul
Lufkin, Nathaniel H. ..... Minneapolis
Luh, Edwin F. ..... St. Paul
Lukk, Olaf ..... Prior Lake
Lund, Carl J. T. ..... Fergus Falls
Lund, George W. ..... Minneapolis
Lund, J. Benjamin ..... Mankato
Lund, Nancy R. ..... Minneapolis
Lund, Richard R. ..... Minneapolis
Lund, Werner J. ..... Staples
† Lundberg, Ruth I. ..... St. Paul
† Lundblad, Roy A. ..... Minneapolis
Lundblad, Rodger R. ..... Minneapolis
Lundblad, Stanley W. ..... Minneapolis
Lundborg, Richard O. ..... Rochester
† Lundeberg, Karl R. ..... Minneapolis
Lundell, Carl L. ..... Granite Falls
Lundholm, Arthur M. ..... Harris
Lundquist, Charles B. ..... Minneapolis
Lundquist, Curt W. ..... Owatonna
Lundquist, Virgil J. ..... Minneapolis
Lundsten, Leslie C. ..... Bemidji
Lunzer, Richard G. ..... St. Paul
Lynch, Francis W. ..... St. Paul
Lynch, Michael F. ..... Minneapolis
Lynch, Miles W. ..... Mt. Prospect, IL
Lynch, Richard P. ..... St. Paul
† Lynde, Orrin G. ..... Los Gatos, CA
Lynn, Hugh B. ..... Rochester
Lynn, Walter ..... Minneapolis
Lyon, Fred A. ..... Minneapolis
Lyon, John D. ..... Hopkins
*† Lyons, Michael ..... Riverside, CA
† Lysne, Henry ..... Minneapolis
Lysne, Richard B. ..... Minneapolis
Lysyj, Anatol ..... Minneapolis
Lyzenga, Anton G. ..... Minneapolis

M

McAfee, David K. ..... Willmar
McBean, James B. ..... Rochester
McCaffrey, F. John ..... Minneapolis
McCain, Donovan L. ..... St. Paul
McCampbell, Malcolm D. ..... Minneapolis
McCannel, Malcolm A. ..... Minneapolis
McCarten, Francis M. ..... Stillwater
McCarthy, Austin M. ..... Willmar
McCarthy, Charles J. ..... St. Paul
† McCarthy, Donald ..... Minneapolis
McCarthy, Laurence J. ..... Honolulu, HI
† McClanahan, Thomas S. ..... White Bear Lake
McClellan, Robert J. ..... St. Paul
McClelland, John G. ..... Virginia
McCloud, C. Naumann ..... St. Paul
† McConahay, David R. ..... Rochester
McConahey, William M., Jr. ..... Rochester
McCormick, Donald P. ..... Minneapolis
McCoy, Donald E. ..... Glencoe
† McDaniel, Orianna ..... Minneapolis
† McDaniel, Samuel P. ..... Lakeville
† McDowell, John P. ..... St. Cloud
McEllistrem, Edward J. ..... St. Paul
McEllistrem, Gerald D. ..... St. Paul
McEnaney, James E. ..... Owatonna
McEwan, Alexander ..... St. Paul
McFarland, Arthur H. ..... Minneapolis
McGandy, Robert F. ..... Minneapolis
*† McGeary, George E. ..... No. Ft. Myers, FL
McGill, Douglas B. ..... Rochester
McGoon, Dwight C. ..... Rochester
McGroarty, Brian J. ..... St. Paul
McHutchison, Samuel K. ..... St. Paul
McIlrath, Donald C. ..... Rochester

McInerny, Maurice W. ..... Minneapolis
† McIntyre, John A. ..... Owatonna
McKelvey, John M. ..... Minneapolis
McKenna, Charles H. ..... Chicago, IL
McKenna, James L. ..... Minneapolis
McKenna, John J. ..... Virginia
† McKenna, Jay K. ..... LaJolla, CA
McKenna, Maurice J. ..... Grand Rapids
McKenzie, Charles H. ..... Minneapolis
McKenzie, Eva E. ..... St. Paul
† McKinlay, Chauncey A. ..... Minneapolis
McKinley, Gordon L. ..... Minneapolis
† McKinney, Frank S. ..... Minneapolis
McLane, William O. ..... Brainerd
McLaughlin, Byron H. ..... Minneapolis
† McLaughlin, Edmund M. ..... Winona
McMahon, John E. ..... Minneapolis
McManus, William F. ..... Princeton
McMurtrie, William B. ..... Minneapolis
McNamara, John P. ..... Rice
* McNear, George R., Jr. ..... Heron Lake
McNeil, John J. ..... Minneapolis
McNeil, Maurice R. ..... Glencoe
McNeill, John A. ..... St. Paul
† McNutt, John R. ..... Duluth
McParland, Felix A., Jr. ..... Minneapolis
† McPheeters, Herman O. ..... Minneapolis
McPherson, James R. ..... Rochester
McQuoid, David W. ..... Littlefork
McRoberts, Jerry W. ..... Bremerton, WA
MacCarty, Collin S. ..... Rochester
MacCornack, Robert L., Jr. ..... St. Paul
† MacDonald, Charles J. ..... Rochester
† MacDonald, Daniel A. ..... Minneapolis
MacDonald, Roger A. ..... Grand Marais
† MacKenzie, Kenneth R. ..... Rochester
MacKinnon, Donald C. ..... Minneapolis
MacLean, Alexander R. ..... Rochester
MacRae, Gordon C. ..... Duluth
† Mach, Frank B. ..... Minneapolis
Mach, John R. ..... Minneapolis
Mach, Ralph F. ..... Pine City
Macheledt, Neil L. ..... Anoka
Macklin, William E. ..... Litchfield
Mackoff, Samuel ..... Phoenix, AZ
Madland, Robert S. ..... St. Paul
Madsen, Donald O. ..... Minneapolis
Maeder, Edward C. ..... Minneapolis
† Maeder, Edward C., Jr. ..... St. Paul
Magary, Victor J., Jr. ..... Ft. Campbell, KY
† Magath, Thomas B. ..... Rochester
Magid, Gail A. ..... Santa Cruz, CA
† Magnant, Henry ..... Rochester
Magness, John L. ..... Rochester
† Magney, Fredolph H. ..... Duluth
Magnuson, Allen E. ..... Wheaton
Magnuson, Raymond C. ..... Cambridge
Magraw, Richard M. ..... Silver Spring, MD
Maher, Frank T. ..... Rochester
Mahle, Donald G. ..... Wabasha
Mahle, James P. ..... Minneapolis
Mair, Douglas D. ..... Goldsboro, NC
Maitland, Edwin T. ..... Jackson
† Maland, Clarence O. ..... Minneapolis
Maldonado, Jorge E. ..... Rochester
Malerich, J. Anthony ..... West St. Paul
Malkasian, George D. ..... Rochester
Malmquist, Carl P. ..... Minneapolis
Mandel, Sheldon L. ..... Minneapolis
Manick, Kenneth P. ..... Minneapolis
Mankey, James C. ..... Minneapolis
Mankin, Harold T. ..... Rochester
Manlove, Charles H., Jr. ..... St. Paul
Mann, George A. ..... Minneapolis
Manoles, Elias N. ..... Minneapolis
MarCia, Alfred M. ..... Minneapolis
Marcoux, J. Paul ..... Bethesda, MD
Mark, Aaron L. ..... Minneapolis
Mark, Merle S. ..... Minneapolis
Marking, George H. ..... Minneapolis
Markland, A. Colin ..... Minneapolis
Markovitz, Jack M. ..... Minneapolis
Marshall, Clark M. ..... Crosby
Marso, John L. ..... Mankato
Marta, John B. ..... St. Paul
Marte, Egon ..... Minneapolis
Martens, Theodore G. ..... Rochester
Martin, Albert C. ..... Luverne
Martin, David E., III ..... Wabasha
Martin, Doreen A. ..... Pepin, WI
Martin, Dwight L. ..... St. Paul
Martin, Frank E. ..... Minneapolis
Martin, George B. ..... Thief River Falls
Martin, George R. ..... Minneapolis
Martin, Gordon M. ..... Rochester
Martin, Harold R. ..... Rochester
Martin, John T. ..... Rochester
Martin, Maurice J. ..... Rochester
Martin, Webster C. ..... Duluth
Martin, William J. ..... Rochester
† Martineau, Joseph L. ..... St. Paul
Martinson, Carl J. ..... Wayzata
Martinson, Elmer J. ..... Wayzata
Martinson, Raymond M. ..... Virginia
† Martyn, David T. ..... Rochester
Marvin, Joseph E. ..... Brainerd
Maryland, Daniel L. ..... Duluth
Maslansky, Robert A. ..... Minneapolis
Massee, Joseph S. ..... Minneapolis
† Masson, Duncan M. ..... Rochester
† Masson, James C. ..... Rochester
Masson, James K. ..... Rochester
Mast, Frederic L. ..... Chisholm
Mastan, Peter F. ..... APO New York, NY
Mateo, Guillermo ..... St. Paul
Mathers, John E. ..... Austin
Mathews, Wallace ..... Mankato
Mathieson, Don R. ..... Rochester
Mathison, Robert D. ..... Plainview
Matthews, James H. ..... Minneapolis
Mattison, Percy A. ..... Winona
Mattson, Albert D. ..... St. James
Mattson, Donald S. ..... Willmar
Mattson, Hamlin A. N. ..... Minneapolis
Matus, Richard N. ..... St. Paul
Maunder, John B. ..... Minneapolis
Maupin, Roger A. ..... San Francisco, CA
Maus, Donald J. ..... Monticello
Maus, Philip W. ..... Dawson
† Maxeiner, Stanley R. ..... Minneapolis
Maxeiner, S. R., Jr. ..... Minneapolis
May, Robert B. ..... St. Cloud
Mayberg, Donald M. ..... Minneapolis
Mayne, John G. ..... Rochester
† Mayne, Roy M. ..... St. Paul
† Mayo, Charles W. ..... Rochester
Mazzitello, William F. ..... St. Paul

Meany, Thomas J. ..... Minneapolis
Mears, Burtis J. ..... St. Paul
Mecklenburg, Fred E. ..... Minneapolis
Medelman, John P. ..... St. Paul
Meeker, Henry C. ..... Minneapolis
Meekin, Patrick C. ..... Minneapolis
† Meinert, Albert E. ..... Winona
Meinert, John K. ..... Willmar
Melancon, Joseph F. ..... St. Paul
Meller, Maurice ..... Brainerd
Meller, Robert L. ..... Minneapolis
Mendesh, Anthony N. ..... Duluth
Mendiola, Ramon P., Jr. ..... Waconia
Menefee, Edward C. ..... Albert Lea
Mensheha, Nicholas M. ..... Minneapolis
Mercil, Charles B. ..... Mahnomen
Mercil, William F. ..... Crookston
Meredith, Donald C. ..... Mankato
Merner, Thomas B. ..... Minneapolis
† Merrick, Charlotte T. ..... St. Paul
Merrick, Robert L. ..... St. Paul
Merrick, William G. ..... Duluth
Merrill, Robert ..... Des Moines, IA
Merritt, Wallace A. ..... Rochester
† Mertens, Benny F. ..... Rochester
† Mess, Charles F. ..... Rochester
Messenheimer, Myron G. ..... Minneapolis
† Metcalf, Norman B. ..... Princeton
Metz, Donald D. ..... Minneapolis
Meyer, Alvin J. ..... Minneapolis
† Meyer, E. Lawrence ..... Winona
Meyer, Frederick C. ..... Kenyon
Meyer, Howard J. ..... Duluth
Meyer, Melvin E. ..... Rochester
Meyer, Paul F. ..... Faribault
Meyer, Richard H. ..... Faribault
Meyer, Robert P. ..... Faribault
† Meyerding, Henry W. ..... Rochester
† Michael, Joseph C. ..... Minneapolis
Michaelis, Dorothy L. ..... Duluth
Michel, Henry H. ..... Minneapolis
† Michels, Roger P. ..... Willmar
† Michelson, Henry E. ..... Minneapolis
Michienzi, Leonard J. ..... St. Paul
† Mickelsen, Emma F. (Fronk) ..... Minneapolis
Mickelson, John C. ..... Los Angeles, CA
Middlebrook, John E. ..... Minneapolis
Midthune, Andreen S. ..... Lake Park
Miettunen, John B. ..... Hibbing
Miks, George M. ..... Aurora
Miller, Albert G. ..... St. Paul
Miller, Alfred ..... Sheppard AFB, TX
† Miller, Charles H., III ..... Minneapolis
† Miller, Donald R. ..... Rochester
† Miller, Gerald J. ..... Minneapolis
Miller, H. Dawes ..... Minneapolis
Miller, Harold E. ..... Minneapolis
Miller, Herman ..... Austin
Miller, Hugo E. ..... Minneapolis
Miller, J. Carleton ..... Minneapolis
Miller, John W., Jr. ..... Louisville, KY
Miller, Roland D. ..... Rochester
Miller, Ross H. ..... Rochester
Miller, William P. ..... Minneapolis
Miller, Winston R. ..... St. Paul
Miller, Zondal R. ..... St. Paul
Millett, D. Keith ..... Minneapolis
Millikan, Clark H. ..... Rochester
† Mills, John L. ..... Winnebago
Mills, Stephen D. ..... Rochester
Milnar, Frank J. ..... St. Paul
Milroy, Thomas W. ..... Minneapolis
Milton, John S. ..... Minneapolis
Minder, John G. ..... Minneapolis
Minge, Raymond K. ..... Worthington
Minsky, Armen A. ..... Minneapolis
Mishek, Charles J. ..... St. Paul
Mitby, Irvin L. ..... Minneapolis
Mitchell, Berton D. ..... Minneapolis
Mitchell, Edward C. ..... Mound
Mitchell, George S. ..... St. Paul
Mitchell, John S. ..... Seoul, Korea
Mitchell, Mancel T. ..... Minneapolis
Mixer, Harry W. ..... Minneapolis
Mlinar, Joseph P. ..... Austin
Moberg, Clarence W. ..... Detroit Lakes
Mock, Charles J. ..... Virginia
† Mockert, Thomas, Jr. ..... Rochester
Moe, John H. ..... Minneapolis
† Moe, Thomas ..... Moose Lake
Moe, W. Wyatt ..... Minneapolis
Moehn, John T. ..... Minneapolis
Moeller, Henry G., Jr. ..... Charleston, SC
Moen, Johannes K. ..... Minneapolis
† Moersch, Frederick P. ..... Ft. Lauderdale, FL
† Moersch, Herman J. ..... Rochester
Moertel, Charles G. ..... Rochester
Moffitt, Emerson A. ..... Rochester
† Molander, Herbert A. ..... St. Paul
Molenaar, Robert E. ..... Cannon Falls
Moller, Julie C. ..... Duluth
Moller, Jurgen ..... St. Paul
Mollers, Theodore P. ..... Ft. Snelling
Molnar, George D. ..... Rochester
Monahan, Robert H. ..... St. Paul
Mongé, James J. .....Duluth
Monserud, Nels O. ..... Cloquet
Monson, Einer M. ..... Minneapolis
Monson, Leonard J. ..... Canby
Monson, Warren A. ..... Minneapolis
† Montgomery, Hamilton ..... Rochester
Mooney, Robert D. ..... St. Paul
Moore, Gordon L., II ..... Rochester
† Moore, Irvin H. ..... Hopkins
Moorhead, Marie ..... Minneapolis
Moos, Daniel J. ..... Minneapolis
Moral, Harvey M. ..... Minneapolis
Moran, Leo J. ..... New Brighton
Moran, Paul T. ..... St. Cloud
† Morehead, Dewey E. ..... Bodega Bay, CA
Moren, J. Adelaide ..... St. Paul
Morgan, Hugh O. ..... Amboy
† Morgan, Stephan S. ..... Rochester
Mori, Hideo ..... Grand Meadow
Moriarty, James A. ..... Minneapolis
Moriarty, Joseph D. ..... Coon Rapids
Mork, A. Harold ..... Anoka
Mork, Frank E. ..... Anoka
Mork, Frank E., Jr. ..... Minneapolis
Morlock, Carl G. ..... Rochester
Morrison, Charlotte J. ..... Minneapolis
Morrow, George W., Jr. ..... Rochester
† Morse, Morton P. ..... LeRoy
Morse, Robert M. ..... Rochester
Morse, Roger D. ..... LeRoy
† Mortensen, Nels G. ..... St. Paul
Mortenson, Howard O. ..... Menahga
Mosby, Maurice E. ..... Long Prairie

Moss, Nyel H. ..... St. Paul
Mosser, Donn G. ..... Minneapolis
Moulton, Keith B. ..... St. James
Mouritsen, Glenn J. ..... Fergus Falls
Moyer, John B. ..... Duluth
Moyer, Leonard B. ..... Minneapolis
Moyer, Richard R. ..... Hibbing
Muchmore, Harold G. ..... Oklahoma City, OK
Muchow, Gene C. ..... Austin
Mueller, Donald R. ..... Grand Rapids
Mueller, LeRoy E. ..... Hendricks
Mueller, Rudolph B. ..... Richmond
Muesing, Mark A. ..... Tyler
Muesing, William J. ..... New Ulm
Mulder, Donald W. ..... Rochester
Mulholland, William M. ..... Minneapolis
Muller, A. Eugene ..... North St. Paul
Muller, John J. ..... Hibbing
Muller, Sigfrid A. ..... Rochester
Mulligan, Arthur M. ..... Brainerd
Mullin, Gerald T., Jr. ..... Minneapolis
Mulvahill, John E. ..... Minneapolis
Mundahl, Harold R. ..... St. Paul
Munger, James E. ..... Duluth
Munkittrich, Ronald C. ..... Minneapolis
Munneke, Lyle ..... Clara City
Munson, Martin S. ..... Moose Lake
Murn, Thomas G. ..... St. Cloud
Murphy, Edmund P. ..... Minneapolis
Murphy, Jack T. ..... St. Paul
Murphy, Joseph E. ..... Marshall
Murphy, Thomas R. ..... Stillwater
Murray, Elisabeth M. ..... Minneapolis
Murray, Robert A. ..... Hibbing
Murray, Robert A., Jr. ..... St. Cloud
Murray, Roger C. ..... St. Paul
Musachio, Nicholas F. ..... St. Paul
Muske, Marvin M. ..... Minneapolis
Mussey, Mary E. ..... Rochester
Musty, Nicholas J. ..... Minneapolis
† Myers, George H., Jr. ..... Rochester
Myers, Jay A. ..... Minneapolis
Myers, John W. ..... Canby
Myers, Theodore P. ..... Albert Lea
Myers, Thomas T. ..... Rochester
† Myers, Thomas T., III ..... Rochester
Myhre, James A. ..... Minneapolis
† Mylrea, Murray J. ..... Bloomington
Myre, Clifford R. ..... Paynesville

N

† Nadeau, Claude .... Trois-Rivieres, Quebec, Canada
Nagobads, Ilgvars J. ..... Minneapolis
Nagobads, V. George ..... Minneapolis
Najarian, John S. ..... Minneapolis
Nash, Eldore B. ..... Minneapolis
* Naslund, Ames W. ..... Minneapolis
† Nathan, Fred F. ..... Rochester
Nauth, Bernard S. ..... Scottsdale, AZ
Navratil, Donald R. ..... Glencoe
† Neal, Joe M. ..... Minneapolis
Nealy, Donald E. ..... Adrian
Nealy, Timothy E. ..... Blooming Prairie
Neary, Richard P. ..... Minneapolis
Neault, Roger W. ..... Rochester
Neel, Harry B. ..... Albert Lea
Neff, Walter S. ..... Britt
Neher, Frederick J. ..... St. Paul
Nehring, John ..... Wabasha
Neils, Vernon E. ..... St. Cloud
Nelimark, Donald R. ..... Virginia
† Nelson, Audrey M. ..... Rochester
† Nelson, Bernette G. ..... Slayton
† Nelson, Bernice A. ..... Minneapolis
Nelson, C. Barton ..... Minneapolis
Nelson, Carleton A. ..... Minneapolis
Nelson, Clayton E. J. ..... Albert Lea
Nelson, David J. ..... Minneapolis
Nelson, Delbert R. ..... St. Paul
Nelson, Edward N. ..... Minneapolis
Nelson, Evan L. J. ..... Minneapolis
Nelson, George E. ..... Minneapolis
Nelson, Gerald E. ..... Chaska
Nelson, Glenn E. ..... Fairfax
Nelson, Gunard A. ..... Minneapolis
† Nelson, Harvey ..... Pampano Beach, FL
† Nelson, Henry E. ..... Crookston
Nelson, J. Phillip ..... Millington, TN
Nelson, Lloyd S. ..... Minneapolis
Nelson, Loren E. ..... St. Paul
Nelson, Louis A. ..... St. Paul
Nelson, Luther A. ..... Rush City
Nelson, Maxine O. ..... Minneapolis
Nelson, Maynard C. ..... Minneapolis
Nelson, O. L. Norman ..... Minneapolis
Nelson, Robert H. ..... Benson
† Nelson, Rodger K. ..... Rochester
Nelson, Ronald J. ..... St. Paul
Nelson, Roy A. ..... Fergus Falls
Nelson, Wallace I. ..... Minneapolis
Nerenberg, Sidney ..... Minneapolis
Nesheim, Martin O. ..... Emmons
Ness, Duane E. ..... Wadena
Ness, Richard A. ..... Fergus Falls
Neese, James A. ..... Austin
Nesset, Lawren B. ..... Minneapolis
Nesset, William D. ..... Minneapolis
Nesvacil, Leon ..... St. Paul
† Nettles, Joe L. ..... Rochester
Neumaier, Arthur ..... Glencoe
Neumann, Roland F. ..... Minneapolis
Neumeister, Charles A. ..... Minneapolis
Neuwirth, Gerardo D. ..... Minneapolis
Newcomer, Albert D. ..... San Diego, CA
Niazi, Suad A. ..... Granite Falls
Nicholas, S. Scott, Jr. ..... Minneapolis
Nichols, Donald R. ..... Rochester
Nichols, Thomas O. ..... St. Paul
Nicholson, Richard W. ..... Fergus Falls
Nickerson, John R. ..... Fairmont
Nickerson, Neil D. ..... Fairmont
Nicolay, William R. ..... Red Wing
Nielsen, David J. ..... Minneapolis
Nietfeld, Aloys B. ..... Sauk Centre
Nilsen, John A. ..... Minneapolis
Nimlos, Kenneth O. ..... St. Paul
† Nimlos, Lenore O. ..... St. Paul
Nisius, George F. ..... Duluth

Nisswandt, Albert L. ..... Duluth
Nixon, James B. ..... Crosby
† Nobrega, Fred T. ..... Rochester
† Nolan, Alfred C. ..... Rochester
Nolan, Robert K. ..... Minneapolis
Nolen, William A. ..... Litchfield
Nollet, Donald J. ..... Hibbing
Noran, Harold H. ..... Minneapolis
† Norberg, Carl E. ..... Los Altos, CA
Nord, Robert E. ..... Minneapolis
† Nordin, Gustaf T. ..... Kaneohe, HI
† Nordland, Martin ..... Minneapolis
Nordman, Willard F. ..... Mora
Noren, George R. ..... Minneapolis
Norman, David D. ..... St. Paul
Norman, Mark L., Jr. ..... Minneapolis
Normann, Stephen T. ..... Waseca
Norquist, Joseph L. ..... Waseca
Norval, Mildred A. ..... Minneapolis
Nuebel, Charles J. ..... Long Beach, CA
† Nuessle, Walter G. ..... Springfield
Nuessle, William F. ..... Minneapolis
Nuetzman, Arthur ..... Faribault
Nydahl, Bruce C. ..... Minneapolis
Nydahl, Malvin J. ..... Minneapolis
† Nye, Lillian L. ..... St. Paul
Nygren, William T. ..... Braham
Nywall, Dean D. ..... Slayton

O

O'Brien, Bruce J. ..... Minneapolis
O'Brien, Gerald R. ..... Minneapolis
O'Brien, John C. ..... St. Paul
O'Brien, Louis T. ..... Breckenridge
O'Brien, William A. ..... Minneapolis
O'Connell, Edward J. ..... March AFB, CA
† O'Donnell, James E. ..... Minneapolis
O'Kane, Thomas W. ..... St. Paul
O'Keefe, James P. ..... St. Cloud
O'Leary, John B. ..... Brainerd
O'Malley, Valentine ..... St. Paul
O'Neil, Bernerd L. ..... Minneapolis
O'Neill, John C. ..... Duluth
O'Neill, Nial C. ..... St. Paul
O'Phelan, E. Harvey ..... Minneapolis
† O'Reilley, Bernard E. ..... Sun City, AZ
O'Rourke, William J. ..... Austin
† O'Sullivan, Michael B. ..... Rochester
Oberstein, Barry J. ..... Rantoul, IL
† Obetz, Samuel W. ..... Rochester
Ochsner, Clarence G. ..... Santa Barbara, CA
Ockuly, Orville E. ..... St. Paul
Odland, Donald M. ..... Luverne
Odland, Mark E. ..... Detroit Lakes
Odland, Olin M. ..... Granite Falls
† Odyniec, Norman A. ..... Rochester
Oeljen, Siegfried C. ..... Waseca
† Oels, Helen C. ..... Rochester
Officer, Charles D. ..... Burnsville
† Ogden, Warner ..... St. Paul
† Ohage, Justus ..... St. Paul
Ohmann, Ronald ..... Glencoe
† Okeson, Gyman C. ..... Rochester
Olavs, Olga ..... Minneapolis
Olds, George H. ..... New Richland
Olfelt, Paul C. ..... Minneapolis
Olinger, John N. ..... St. Cloud
Olive, John T., Jr. ..... Mankato
Olmanson, Edmund G. ..... St. Peter
Olmanson, M. Donald ..... St. Peter
Olmanson, Vern C. ..... St. Peter
Olsen, Arthur M. ..... Rochester
Olsen, E. George ..... Minnetonka
Olsen, Jay R. ..... Minneapolis
Olsen, Ralph L. ..... St. Paul
Olson, Albert J. ..... Owatonna
Olson, Alton C. ..... Minneapolis
Olson, Barbara F. ..... Minneapolis
Olson, C. Kent ..... Minneapolis
Olson, Carl J. ..... Minneapolis
Olson, Detlof M. ..... Minneapolis
Olson, Duane C. ..... Minneapolis
Olson, Frances P. ..... Fergus Falls
Olson, Grant E. ..... West Concord
Olson, Gregory M. ..... Litchfield
Olson, Hardin E. ..... Minneapolis
Olson, Lillian A. ..... Ah-Gwah-Ching
† Olson, Neal R. ..... Rochester
† Olson, Olof A. ..... Minneapolis
Olson, Philip A. ..... Minneapolis
Olson, Richard E. ..... Chaska
Olson, Robert E. ..... Minneapolis
Olson, Robert T. ..... Canby
Olson, Robert W. ..... Minneapolis
Olson, Rolland A. ..... Wayzata
Ongley, Patrick A. ..... Rochester
Onofrio, Burton M. ..... Rochester
† Onsgard, L. Kenneth ..... St. Petersburg, FL
Onstad, Gerald R. ..... Fort Rucker, AL
† Onstad, Thomas A. ..... Rochester
Opheim, Richard H. ..... Minneapolis
Opitz, Joachim L. ..... Rochester
Oppegaard, C. L. ..... Scottsdale, AZ
Oppen, E. Gerhard ..... Minneapolis
Oppen, Melvin G. ..... Minnetonka
Opsahl, Lawrence J. ..... Willmar
Opstad, Earl T. ..... Minneapolis
Orandi, Ahmad ..... Fergus Falls
Orandi, Mehdi ..... Fergus Falls
Orbuch, Martin W. ..... Minneapolis
Orkin, Milton ..... Minneapolis
Orr, Burton A. ..... Faribault
Osekowsky, Henry J. ..... St. Paul
Osmundson, Philip J. ..... Rochester
Osterberg, Kenneth A. ..... Minneapolis
† Ostergaard, Erling ..... Elbow Lake
† Ostergren, Edward W. ..... St. Paul
Ott, Eugene C. ..... Minneapolis
Ouellette, Alfred J. ..... St. Paul
† Ourada, Anthony L. ..... St. Paul
† Overby, Philip G. ..... Minneapolis
Owen, Charles A., Jr. ..... Rochester
Owen, Richard R. ..... Minneapolis
Owens, Ben P. ..... Hibbing
Owens, Frederick M. ..... St. Paul
Owens, William A. ..... Montevideo

P

Paal, Dwain J. ..... Minneapolis
Paciotti, Vincent J. ..... Hibbing
Page, Raymond L. ..... Minneapolis
† Pairolero, Peter C. ..... Rochester
Paisner, Hyman M. ..... Minneapolis
Palen, Benjamin J. ..... Scottsdale, AZ
Palm, E. Theodore ..... Minneapolis
Palm, Neil M. ..... St. Paul
Palmer, Clinton F. ..... Albert Lea
Palmer, Harry A. ..... Blackduck
Palumbo, Pasquale J. ..... Rochester
Paparella, Michael M. ..... Minneapolis
Papermaster, Ralph ..... Minneapolis
Papermaster, Theodore C. ..... Wayzata
Pappas, George ..... Denver, CO
Paris, Jaime ..... Rochester
Park, Wilford E. ..... Minneapolis
Parker, Charles W. ..... Wadena
† Parker, Joseph C., Jr. ..... Rochester
Parker, Robert L. ..... Rochester
Parker, Warren E. ..... Sebeka
Parker, Wilbert H. ..... Chisholm
† Parkhill, Edith M. ..... Rochester
Parkin, Thomas W. ..... Rochester
Parod, John D. ..... Minneapolis
Parrott, John C. ..... Minneapolis
Parson, E. Irvine ..... Duluth
†* Parson, Lester R. ..... Elbow Lake
Parsons, R. A. ..... St. James
Parsons, Ralph L. ..... Trimont
Parsons, William R. ..... Portland, OR
Pasek, Antone W. ..... Cloquet
Patch, Orien B. ..... Duluth
Pattee, James J. ..... Minneapolis
Patten, John C. ..... Austin
Patterson, Hugh D. ..... Slayton
Patterson, Paul G. ..... Minneapolis
† Patterson, William L. ..... Fergus Falls
Paule, William J. ..... Minneapolis
Paulson, Elmer C. ..... St. Paul
Paulson, John A. ..... Rochester
Paulson, Wallace J. ..... St. Paul
Payne, Richard E. ..... Virginia
Payne, Robert A. ..... Athens, GA
† Payne, Stanley R. ..... Rochester
Payne, W. Spencer ..... Rochester
Peacock, William F., III ..... Littleton, CO
Peake, Janna Z. ..... Minneapolis
Pearson, Bror F. ..... Shakopee
† Pearson, Fritz R. ..... St. Paul
Pearson, Harris L. ..... Bagley
Pearson, Malcolm M. ..... St. Paul
† Pease, Gertrude L. ..... Rochester
† Pedersen, Arthur H. ..... St. Paul
Pedersen, Robert L. ..... Brainerd
Pedersen, Roy C. ..... Duluth
Peiper, Warren S. ..... Minneapolis
Peluso, Charles R. ..... Minneapolis
Pelzl, Charles R. ..... Pine River
*† Pemberton, John deJ. ..... Rochester
Penk, Engward L. ..... Springfield
Penn, George E. ..... Mankato
Pennington, Mary ..... Minneapolis
Peper, Martin C. ..... Minneapolis
Perkins, Douglass E. ..... Alexandria
Perlman, Everett C. ..... Minneapolis
Perlman, Herschel L. ..... St. Louis Park
Perpich, Irene Kosiak ..... Virginia
Perry, Harold O. ..... Rochester
Perry, John F., Jr. ..... St. Paul
Person, Duane F. ..... Virginia
Pesonen, Clifford ..... Austin
Peteler, Jennings C. L. ..... Minneapolis
Peters, Gustavus A. ..... Rochester
Petersen, Bryon D. ..... Minneapolis
Petersen, Dean A. ..... Wayzata
Petersen, Donald H. ..... Willmar
Petersen, Glenn L. ..... Minneapolis
Petersen, Magnus C. ..... Rochester
Petersen, Robert T. ..... St. Cloud
Petersen, William E. ..... Minneapolis
Peterson, Alvin C. ..... Mora
Peterson, Charles A. ..... Minneapolis
Peterson, Donald H. ..... St. Paul
Peterson, Edward A. ..... St. Paul
Peterson, Edward N. ..... Virginia
Peterson, Hamlet A. ..... Rochester
Peterson, Harold O. ..... Minneapolis
Peterson, Joel L. E. ..... St. Paul
Peterson, John A. ..... Minneapolis
Peterson, John H. ..... Duluth
Peterson, John O. H. ..... Hastings
Peterson, John R. ..... Rushford
Peterson, Kenneth A. ..... Marshall
Peterson, Kenneth H. ..... Hutchinson
Peterson, Lowell F. A. ..... Rochester
Peterson, Oliver H., Jr. ..... Minneapolis
Peterson, Palmer A. ..... Minneapolis
Peterson, Richard A. ..... Seattle, WA
Peterson, Roy A. ..... Vesta
Peterson, Roy L. ..... White Bear Lake
Peterson, Stanley C. ..... Austin
Peterson, Theodore A. ..... Minneapolis
† Peterson, Willard C., Sr. ..... Minneapolis
Peterson, Willard C., Jr. ..... Minneapolis
Peterson, Willard E. ..... Willmar
Peterson, Willard H. ..... Minneapolis
Petit, Julien V. ..... Minneapolis
† Petit, Leon J. ..... Minneapolis
Petraborg, Harvey T. ..... Aitkin
Pettersen, George R. ..... Aitkin
Pewters, John T. ..... Minneapolis
Peyla, Thomas L. ..... Rochester
Pfohl, Richard A. ..... Minneapolis
Phares, Otto C. ..... St. Cloud
† Phelps, Kenneth A. ..... St. Petersburg, FL
Phelps, Robert D. ..... Minneapolis
Phibbs, Clifford M., Jr. ..... Minneapolis
Phillips, Leonard ..... St. Paul
Philp, David R. ..... Watertown
Pierce, Robert B. ..... Heron Lake
Pierre, Robert V. ..... Rochester
Pierson, Roy F. ..... Slayton
Pilling, Loran F. ..... Rochester
Pincus, Mitchell ..... Minneapolis
† Pingree, George C. ..... Rochester
† Piper, William A. ..... Mountain Lake
Pistulka, Rolland D. ..... Chaska
Pitcher, Arlo L. ..... St. James

Pivac, Dragojla (Popovich) ..... Milwaukee, WI
Plasha, Matthew K. ..... Coon Rapids
Plass, Herbert F. R. ..... Minneapolis
Plimpton, Nathan C. ..... Minneapolis
Plotke, Harry L. ..... St. Paul
Plucker, Milton W. ..... Worthington
† Plummer, Alan L. ..... Rochester
† Pluth, James R. ..... Rochester
Pohl, John F. ..... Minneapolis
† Poirier, Joseph A. ..... White Bear Lake
Polesky, Herbert F. ..... Minneapolis
Poley, Brooks J. ..... Minneapolis
Pollak, Kurt ..... Minneapolis
Pollard, William S. ..... Duluth
Polley, Howard F. ..... Rochester
Pollman, Stanley E. ..... Naha, Okinawa
Pollock, Anthony J. ..... Minneapolis
Polski, Paul G. ..... South St. Paul
Polzak, Jacob A. ..... Minneapolis
Pone, John J. ..... Minneapolis
Ponterio, James E. ..... Shakopee
Pool, T. Lloyd ..... Rochester
Popadiuk, Peter ..... Minneapolis
Popoff, Russel G. ..... Graceville
Popowich, John G. ..... Minneapolis
† Poppe, Frederick H. ..... Miami, FL
Poppie, Robert W. ..... Brainerd
*† Porter, Oliver M. ..... Minneapolis
Post, Edmund A. ..... St. Paul
Poston, Lawrence M. ..... Caledonia
Potter, Robert B. ..... Minneapolis
Power, John E. ..... Duluth
Powers, Robert L. ..... St. Paul
*† Pratt, Fred J., Sr. ..... Minneapolis
Pratt, Fred J., Jr. ..... Minneapolis
Pratt, Joseph H., Jr. ..... Rochester
† Prentice, Walter B. ..... St. Paul
Prem, Konald A. ..... Minneapolis
Preston, Frank S., Jr. ..... Minneapolis
Price, William E. ..... Minneapolis
Prickman, William E. ..... Minneapolis
Priest, Robert E. ..... Minneapolis
Priestley, James T. ..... Rochester
† Prim, Joseph A. ..... Minneapolis
Prlina, Isaac M. ..... Virginia
Proeschel, Ray K. ..... Willmar
* Proffitt, William E. ..... Minneapolis
Proshek, Lumir C. ..... Minneapolis
Proud, Harry S. ..... St. Paul
Provence, Cecil L. ..... Waconia
Pruitt, Raymond D. ..... Rochester
Pugh, David G. ..... Rochester
Pulec, Jack Lee ..... Rochester
Pumala, Erven E. ..... Warren
Purnell, Don C. ..... Rochester
Purves, G. Harland ..... Buffalo
Puumala, Barbara M. ..... Cloquet
Puumala, Reino H. ..... Cloquet
Puumala, Ricard R. ..... Cloquet

Q

Quattlebaum, Frank W. ..... St. Paul
Quello, Robert O. B. ..... Minneapolis
Quiggle, Arthur B. ..... Minneapolis
Quist, Henry W., Jr. ..... Minneapolis

R

Raab, David E. ..... Minneapolis
Raaen, Olaf J. ..... St. Paul
Rabcevich, Anatole ..... St. Paul
Racer, Harley J. ..... Minneapolis
Radke, Robert L. ..... Montevideo
Raetz, Sylvester J. ..... Maple Lake
Raich, John J. ..... Minneapolis
Raile, Richard B. ..... Minneapolis
Ralph, James R. ..... St. Paul
Ralston, Donald E. ..... Rochester
Ramlow, Ralph M. ..... West St. Paul
† Ramsey, Walter R. ..... St. Paul
Randall, David A. ..... Minneapolis
† Randall, Lawrence M. ..... Rochester
Randall, Raymond V. ..... Rochester
Ransom, H. Robert ..... Osseo
Rasmussen, Ramby C. ..... St. Paul
Ratelle, Alexander E. ..... Minneapolis
Raths, Otto N., Jr. ..... St. Paul
Ravits, Harold G. ..... St. Paul
† Rawls, William E. ..... Houston, TX
Rayner, Ralph R. ..... Red Wing
Rea, Charles E. ..... St. Paul
Reardon, Andrew E. ..... Duluth
Recht, Thomas M. ..... Minneapolis
Redfield, Nicholas P. ..... Rochester
Redleaf, Paul D. ..... St. Paul
Reeber, Erick ..... Bagley
Reece, Richard L. ..... Minneapolis
Reed, Henry H. ..... Duluth
† Reed, John H., Jr. ..... Rochester
Reed, Paul ..... Virginia
Reed, Sheldon C. ..... Minneapolis
Reese, David F. ..... Rochester
Reeves, Bradford F. ..... APO 96377
Reff, Alan R. ..... Crookston
Regan, John J. ..... Minneapolis
† Regnier, Edward A. ..... Minneapolis
Reichel, Samuel M. ..... Minneapolis
Reichelderfer, Charles F. ..... Staples
Reichelt, Leland G. ..... Wadena
Reid, Howard C. ..... Bemidji
Reid, James W. ..... South St. Paul
Reid, William O. ..... Willmar
Reif, Harold A. ..... Minneapolis
Reif, Robert W. ..... White Bear Lake
Reiher, Jean ..... Rochester
Reiley, Richard E. ..... Minneapolis
† Reilly, William F., Jr. ..... Rochester
Reiners, Gary ..... Cambridge
Reinhardt, James H. ..... Alexandria
Reiser, Milton P. ..... Minneapolis
Reitemeier, Richard J. ..... Rochester
ReMine, William H., Jr. ..... Rochester

Remole, William D. ..... Minneapolis
† Replogle, William H. ..... Los Angeles, CA
Resch, Joseph A. ..... Minneapolis
Restall, Charles J. ..... Rochester
† Retzlaff, John A. ..... Rochester
Reynolds, James F. ..... Minneapolis
Rhodes, Clinton E. ..... Park Rapids
Rholl, Arnold O. ..... Minneapolis
Rhoton, Albert L., Jr. ..... Rochester
Rice, Carl O. ..... Minneapolis
Rice, Edwin G. ..... Minneapolis
Rice, Fred A. ..... Minneapolis
Rice, Hagbart G. ..... Moorhead
Richards, William B. ..... St. Cloud
Richardson, Edward J., Jr. ..... St. Paul
Richardson, Robert J. ..... Minneapolis
† Richdorf, Lawrence F. ..... Minneapolis
Richter, David J. ..... Virginia
Richter, Paul H. ..... Fergus Falls
Rick, Paul F. W. ..... St. Paul
Rieke, Wellington W. ..... Wayzata
Rieschl, Elizabeth K. ..... Jordan
Riley, Fenwick C. ..... Rochester
Riley, John D. ..... Minneapolis
Riley, William J. ..... Minneapolis
Rimas, Matthew J. ..... Comfrey
Ringhofer, Lawrence ..... New Ulm
Ringle, Otto F. ..... Walker
Rinkey, Eugene ..... St. Paul
Riordan, Elsie M. ..... Minneapolis
Ripple, Rudolph J. ..... St. Paul
Ripple, Rudolph J., Jr. ..... Minneapolis
Risch, Ronald E. ..... Minneapolis
Rissen, Alden F. ..... Stewartville
Ritchie, Donald A. ..... St. Cloud
Ritchie, Wallace P. ..... St. Paul
† Ritt, Albert E. ..... St. Paul
Rizer, Dean K. ..... Minneapolis
Roach, Charles A. ..... St. Paul
Roach, Donald E. ..... St. Paul
† Robb, Edwin F. ..... Minneapolis
Robbins, Owen F. ..... Minneapolis
Roberts, Byron H. ..... Minneapolis
Roberts, George A. ..... Austin
Roberts, Lewis J. ..... Minneapolis
Roberts, Oliver W. ..... Owatonna
Roberts, Stanley W. ..... Minneapolis
Robertson, Dennis M. ..... Rochester
† Robertson, Paul A. ..... Austin
Robinson, Cortland O. ..... Minneapolis
Robinson, William W. ..... Agana, Guam
Rock, William H. ..... Anoka
Rocknem, Robert E. ..... Minneapolis
Rockwell, Curtiss V. ..... Minneapolis
Rockwood, Philo H. ..... Fergus Falls
Rodgers, Richard S. ..... Minneapolis
Roehlke, Arthur B. ..... Elk River
Roemer, Henry J. ..... Winona
Rogers, Charles W. ..... Winona
Rogin, Norton ..... Minneapolis
Rogne, William G. ..... Spring Grove
Roholt, Christian L. ..... McIntosh
Roholt, Hartvig B. ..... Bemidji
† Rohrer, Christian A. ..... Madison Lake
Rohrer, Thomas P. ..... Waseca
† Roland, Charles, Jr. ..... Rochester
Rolig, David H. ..... West St. Paul
Rollie, Orris O. ..... St. Paul
Rollins, Pat ..... Minnetonka
Rome, Howard P. ..... Rochester
Romness, Kenneth B. ..... Mound
Rooke, Edward D. ..... Rochester
Rorem, Joseph A. ..... Appleton
Rosenbaum, David L. ..... Minneapolis
Rosendahl, Frederick G. ..... Minneapolis
† Rosenfield, Abraham B. ..... Minneapolis
Rosenow, Edward C., III ..... Rochester
Rosenow, John H. ..... Minneapolis
Rosenstein, Hanan J. ..... Minneapolis
Rosenthal, F. Harold ..... Austin
† Rosenthal, Robert ..... St. Paul
† Rosenwald, Reuben M. ..... Anoka
Rosevear, John W. ..... Rochester
Ross, James V., Jr. ..... Rochester
Rossberg, Raymond A. ..... Morris
Rossen, Ralph X. ..... Minneapolis
Rossing, Robert G. ..... Brooks AFB, TX
Rotenberg, Robert J. ..... Minneapolis
Rotenberg, Samuel ..... Huntington Park, CA
Roth, Albert H. ..... Deer River
Roth, Frederick D. ..... Mankato
Roth, George C. ..... St. Paul
Rothnem, Morris C. ..... Minneapolis
*† Rothschild, Harold J. ..... St. Paul
Rouse, Henry A. ..... Montevideo
Rovelstad, Randolph A. ..... Rochester
Rowe, Clarence J., Jr. ..... St. Paul
Rowe, Richard G. ..... Silver Bay
† Roy, Paul H. J. ..... Rochester
Roy, Phil C. ..... St. Paul
Rozycki, Anthony T. ..... St. Cloud
Rubin, Jacob S. ..... Crookston
Rubin, Manly ..... Minneapolis
Rubenstein, Mark M. ..... FPO San Francisco, CA
Ruchie, Warren H. ..... Willmar
† Rucker, Charles W. ..... Rochester
Rucker, Thomas K. ..... Minneapolis
† Rucker, William H. ..... Minneapolis
† Rud, Norman E. ..... Edina
Rud, Paul D. ..... Luverne
Rudie, Peter S. ..... Duluth
Rudie, William D. ..... Duluth
Ruggles, George M. ..... Forest Lake
† Ruhberg, George N. ..... Santa Barbara, CA
Ruhe, Albert H. ..... Willmar
Rukavina, John G. ..... St. Paul
† Rulfs, David M., Jr. ..... Rochester
Rumpf, Carl W. ..... Faribault
Runquist, John M. ..... Duluth
Runquist, Richard K. ..... Cambridge
Rushay, Arthur J. ..... White Bear Lake
Rushton, Joseph G. ..... Rochester
Russ, Homer H. ..... Blue Earth
Russ, Homer H., Jr. ..... Warroad
Russell, Thomas J. ..... Barksdale, LA
Russeth, Arthur N. ..... Minneapolis
Rusten, Elmer M. ..... Minneapolis
Rusterholz, Alan P. ..... St. Paul
Ruth, Bradley R. ..... Duluth
Rutledge, John B. ..... Detroit Lakes
† Rutledge, Lloyd H. ..... Detroit Lakes
Ryan, Edward A. ..... Duluth
† Ryan, John J. ..... St. Paul
Ryan, Joseph M. ..... St. Paul
Rydberg, John S. ..... Minneapolis
Rydburg, Wayne C. ..... Minneapolis
† Rydell, Ralph E. ..... Rochester

Ryding, Vincent ..... Ames, IA
Rydland, Arne D. ..... Minneapolis
Rygh, Harold N. ..... Atwater
Rynda, Edwin ..... New Prague
† Rynearson, Edward H. ..... Rochester
Rysgaard, George N. ..... Northfield

S

St. Cyr, Harry M. ..... Minneapolis
St. Cyr, Kenneth J. ..... Minneapolis
† Sabens, James A. ..... Fort Campbell, KY
Sach-Rowitz, Alvan ..... Moose Lake
Saffert, Cornelius A. ..... New U'm
Sakulsky, Stephen B. .... APO San Francisco, CA
Salassa, Robert M. ..... Rochester
Salchert, John J. ..... Minneapolis
Saliterman, Bernard I. ..... Minneapolis
Salk, Richard J. ..... Albany
Saloum, Lucille M. ..... Duluth
Salovich, Edward L. ..... Minneapolis
Salovich, Elmer R. ..... Minneapolis
Salter, Wm. M. ..... Willmar
Salter, Reginald A. ..... Virginia
Sanchez, Jose S. ..... Edina
Sand, Richard E. ..... St. Paul
Sandeen, Robert M. ..... Buffalo
Sander, Frank V., Jr. ..... Rochester
Sander, John L. ..... Cambridge
Sanderson, David J. ..... Fergus Falls
Sanderson, David R. ..... Rochester
Sandkamp, Virgil A. ..... South St. Paul
† Sandok, Burton A. ..... Rochester
Sandt, Karl E. ..... Minneapolis
Sanfelippo, Peter M. .... APO San Francisco, CA
† Sanfilippo, Sylvester J. ..... Minneapolis
Sanford, John B. ..... Duluth
Sanford, Raymond A. ..... Mankato
Sargent, John H. ..... St. Paul
Sartor, Richard ..... Minneapolis
Sather, Edgar L. ..... Fosston
Sather, George A. ..... Fosston
Sather, Richard N. ..... Fosston
Sather, Russell O. ..... Crookston
† Sauer, Jean C. ..... Ft. Snelling
Sauer, William G. ..... Rochester
Savaryn, John P. ..... Waconia
Savelkoul, Gene R. ..... Belgrade
Sawtell, Robert R. ..... Rochester
Sax, Simon G. ..... Duluth
Saxman, Gertrude E. O. ..... Ulen
Sayre, George P. ..... Rochester
Sayther, Keith D. ..... Minneapolis
Sborov, Abe M. ..... Minneapolis
Scallen, Raymond W. ..... Minneapolis
Scanlan, Patrick J. ..... Minneapolis
Scanlon, Hugh A. ..... Little Falls
Scanlon, Paul W. ..... Rochester
Schaar, Frances E. ..... Minneapolis
† Schade, Frederick L. ..... Santa Cruz, CA
Schaefer, Joseph F. ..... Owatonna
Schaefer, Wesley G. ..... Minneapolis
Schafer, Charles F. ..... Winona
Schaffhausen, George E. ..... St. Paul
Schaffhausen, Irwin F. ..... Minneapolis
Schaffhausen, Mildred ..... Minneapolis
Schamber, Walter F. ..... St. Cloud
Schattenberg, Thomas T. ..... Rochester
Scheidel, Alois M. ..... Mankato
*† Scheldrup, N. H. ..... Minneapolis
Scherek, Jerome J. ..... St. Paul
Scherer, L. Raymond ..... Minneapolis
Scherling, Sidney S. ..... Minneapolis
Schiele, Burtrum C. ..... Minneapolis
Schimelpfenig, George T. ..... Chaska
Schirber, Martin J. ..... Grand Rapids
Schirger, Alexander ..... Rochester
Schissel, Gregory A. ..... Minneapolis
† Schlein, Allen P. ..... Rochester
Schloff, Ivan ..... St. Paul
Schloff, Leonard D. ..... St. Paul
Schmid, John F. ..... Duluth
† Schmidt, Hilmar R. ..... Rushford
Schmidt, Paul G. ..... Granite Falls
Schmidt, Ruben F. ..... Alden
Schmidt, W. Robert ..... Minneapolis
Schmidtke, Reinhardt L. ..... St. Paul
† Schmitt, S. C. ..... Fallbrook, CA
Schmitz, Anthony A. ..... Mankato
Schmitz, Everett J. ..... St. Cloud
Schnabel, Robert F. ..... Crookston
Schneck, Jack I. ..... Minneapolis
Schneider, Lawrence E. ..... Duluth
Schneider, Paul J. ..... Adams
Schnell, Frederick S. ..... Litchfield
† Schnur, Paul L. ..... Rochester
† Schoch, Robert B. J. ..... St. Paul
Schochet, H. Laurence ..... St. Paul
† Schoen, Roland F. ..... Rochester
Schoeneberger, P. B. ..... Perham
Schoenfield, Leslie J. ..... Rochester
Schoening, Herbert A. ..... Minneapolis
Schoenwetter, William F. ..... Phoenixville, PA
Scholz, Donald A. ..... Rochester
† Schons, Edward ..... Minnetonka Beach
Schossow, George W. ..... White Bear Lake
Schottler, Jerry L. ..... Fort Leonard Wood, MO
Schottler, Max E. ..... Minneapolis
Schrader, Wayne H. ..... St. Paul
† Schrantz, Robert D. ..... Rochester
Schroeckenstein, Hugo F. ..... St. Paul
Schroeder, Albert J. ..... Minneapolis
Schroeder, Glenn E. ..... Red Wing
Schroeppel, John E. ..... Winthrop
† Schuft, James R. ..... St. Paul
† Schulberg, Verne A. ..... Minneapolis
Schultz, Alvin L. ..... Minneapolis
Schultz, Earl A. ..... Minneapolis
Schultz, J. Harold ..... Minneapolis
Schultz, Peter J. ..... Minneapolis
Schultz, Robert J. ..... Minneapolis
Schulz, Robert W. ..... Fairmont
Schulze, William M. ..... Minneapolis
Schumacher, John W. ..... Minneapolis
† Schut, John W. ..... Anoka
Schwartz, E. Robert ..... Minneapolis
*† Schwartz, Virgil J. ..... Minneapolis
Schweiger, Theodore R. ..... Hibbing
* Schwyzer, Marguerite ..... St. Paul
† Scofield, Edward L. ..... Rochester
Scott, Eugene E. ..... St. Paul

Scott, Horace G. ..... Minneapolis
Scott, Robert H. ..... Minneapolis
Scudamore, Harold H. ..... Rochester
† Seaberg, John A. ..... Pequot Lakes
Searl, Richard H. ..... Faribault
Seay, James E., III ..... Minneapolis
† Sebald, John R. ..... Rochester
Sedlack, Richard E. ..... Rochester
Seecamp, Carsten H. ..... Cambridge
Seery, Thomas M. ..... Austin
Segal, Edward L. ..... Minneapolis
Segal, Martin A. ..... Minneapolis
† Seham, Max ..... St. Paul
Seibel, David I. ..... Minneapolis
Seifert, Donald R. ..... Little Falls
Seifert, Gregory L. ..... Excelsior
Seifert, Milton H. ..... Excelsior
Seifert, Milton H., Jr. ..... Excelsior
Seisler, Edward P. ..... Worthington
Sekhon, Mohan S. ..... St. Paul
Seldon, Thomas H. ..... Rochester
Sells, Richard J. ..... St. Paul
Selmo, Joseph D. ..... Norwood
Semba, Thomas ..... Minneapolis
Semsch, Robert D. ..... Wayzata
† Service, Frederick J. ..... Rochester
Sessler, Alan D. ..... Rochester
Sethre, Arthur E. ..... Fergus Falls
† Setzer, Hobert J. ..... St. Paul
Setzer, Hobert J., Jr. ..... Mankato
Severseike, Odean M. ..... Minneapolis
Severson, Donald R. ..... Minneapolis
† Seybold, Marjorie E. ..... Rochester
Shandorf, James F. ..... Minneapolis
† Shannon, William R. ..... Faribault
† Shaperman, Eva P. ..... La Mesa, CA
Shapiro, Irving ..... Minneapolis
Shapiro, Sidney K. ..... Minneapolis
Shapiro, Stanley W. ..... Minneapolis
Shattuck, Clark A. ..... Minneapolis
Shaver, Ward ..... Fergus Falls
Shaw, Howard A. ..... Minneapolis
Shea, Andrew W. ..... Minneapolis
Shear, Howard H. ..... St. Paul
Shelander, Marcus I. ..... St. Paul
*† Shellman, John L. ..... Pacific Palisades, CA
Shemesh, Alvin ..... Minneapolis
Shepard, Richard ..... Albert Lea
Sheppard, Charles G. ..... St. Peter
Sheps, Sheldon G. ..... Rochester
Sher, David A. ..... Virginia
Sher, Lewis ..... Minneapolis
Sherman, Alfred G. ..... Albert Lea
† Sherman, Carnot H. ..... Bayport
† Sherman, Charles L. ..... Luverne
Sherman, Lloyd F. ..... Minneapolis
* Sherman, Morris H. ..... Minneapolis
Sherman, Roger W. ..... Miami, FL
Sherman, Royal V. ..... Red Wing
Shick, Richard M. ..... Rochester
† Shillington, Maurice A. ..... Ft. Lauderdale, FL
Shin, Rok ..... Howard Lake
Shirley, Raymond M. ..... Duluth
Sholler, Lawrence J. ..... Minneapolis
Short, Marshall H. ..... St. Paul
Shragg, Robert I. ..... Minneapolis
Shronts, John F. ..... Minneapolis
Sidell, Franklin D. ..... Minneapolis
Siebert, Darrel W. ..... Luverne
Siegel, Clarence ..... St. Paul
Siegel, John S. ..... Virginia
Siegmann, William C. ..... Minneapolis
Siekert, Robert G. ..... Rochester
Sigel, Melvin E. ..... Minneapolis
Silas, Ralph M. ..... Minneapolis
Silver, John D. ..... Minneapolis
† Silverman, Louis F. ..... Houston, TX
Silverstein, Murray N. ..... Rochester
Silverstein, Paul M. ..... Minneapolis
Simison, Carl ..... Barnesville
Simmonds, Harry N. L. ..... St. Paul
Simmons, Richard K. ..... Minneapolis
Simo, Kathleen Kay ..... Minneapolis
Simons, John N. ..... Rochester
Simons, Leander T. ..... St. Paul
Simonson, Donald B. ..... Minneapolis
Simonton, Kinsey M. ..... Rochester
† Simpson, Ellery DeW ..... Phoenix, AZ
† Simpson, Thomas E. ..... Rochester
† Sinamark, Andrew ..... Hibbing
Singer, Benjamin J. ..... St. Paul
Sinykin, Melvin B. ..... Minneapolis
Sipe, James W. ..... Coon Rapids
Sisk, Harvey E. ..... St. Cloud
† Sisler, Clifford E. ..... Grand Rapids
Sjoding, J. Donald ..... Mankato
Sjostrom, Lawrence E. ..... St. Peter
Skaife, William F. ..... Benson
Skaug, Harold M. ..... Chatfield
Skinner, Abbott ..... St. Paul
† Skinner, Harvey O. ..... St. Paul
Skjold, Arthur C. ..... Minneapolis
† Skogerboe, Rudolph B. ..... Minneapolis
† Skolnick, Judah L. ..... Rochester
Slack, William J. ..... Duluth
Slanga, Roger A. ..... St. Cloud
Slocumb, Charles H. ..... Rochester
Slosser, Gaius J. ..... Ft. Knox, KY
Smiley, Donald P. ..... St. Paul
Smiley, John T. ..... Minneapolis
Smisek, Elmer A. ..... St. Paul
Smisek, Frank M. ..... Minneapolis
† Smith, Adam M. ..... Minneapolis
Smith, Archie M. ..... Minneapolis
Smith, Barlow ..... Minneapolis
Smith, Baxter A., Jr. ..... Minneapolis
Smith, Cyril M. ..... Duluth
Smith, David E. ..... Washington, DC
Smith, David G. ..... Watertown
Smith, David L. ..... San Diego, CA
Smith, Don V. ..... Blue Earth
† Smith, Frederick L. ..... Rochester
Smith, George R. ..... Lafayette, LA
Smith, George Randall ..... Hutchinson
Smith, Graham G. ..... Minneapolis
Smith, H. Nippert ..... St. Paul
Smith, Harry J. ..... Lake Crystal
† Smith, Harry L. ..... Rochester
Smith, John E. ..... Minneapolis
Smith, J. Weston ..... St. Cloud
Smith, Lloyd A. ..... Willmar
Smith, Lucian A. ..... Rochester
† Smith, Max ..... Rochester
Smith, Nadine G. ..... Minneapolis
Smith, Ralph E. ..... Rochester
Smith, Reginald A. ..... Rochester
Smith, Robert J. ..... Beaverton, OR

Smith, Theodore S. ..... Minneapolis
Smith, Thorsten ..... Faribault
Smith, Vernon D. E. ..... St. Paul
Smith, Wallace R. ..... Grand Marais
Smith, William T. ..... St. Paul
Smorstok, Matthew B. ..... Monticello
Smyth, John J. ..... Lester Prairie
† Smythe, Gwendolyn S. ..... Austin
Smythe, Lowell J. ..... Austin
Snider, Howard R. ..... Mankato
† Snider, James H. ..... Rochester
Snyder, Clifford D. ..... Kiester
† Snyder, George W. ..... St. Paul
Snyker, Omer E. ..... Ely
Soderlind, Ragnar T. ..... Minneapolis
† Sohlberg, Olof I. ..... St. Paul
Soiseth, Robert P. ..... Minneapolis
Solhaug, Samuel B., Jr. ..... Minneapolis
Soll, Donald J. ..... Minneapolis
† Solsem, Frederick N. S. ..... Spicer
Solvason, Harold M. ..... Minneapolis
Sommer, Robert K. ..... Elk River
Sommerdorf, Vernon L. ..... St. Paul
Sommers, Stephen D. ..... St. Cloud
Sones, Donald A. ..... Rochester
Sonnesyn, Nels N. ..... Le Sueur
Sontag, David W. ..... Lake City
Sorem, Milton B. ..... St. Paul
Soucheray, Philip H. ..... St. Paul
Soule, Edward H. ..... Rochester
† Souster, Benjamin B. ..... St. Paul
Sowada, Ernest J. ..... St. Paul
Spagnolo, Anthony A. ..... Shakopee
Spain, W. Thomas ..... Evansville, IN
Spang, Anthony J. ..... Duluth
Spang, James S. ..... Duluth
Spang, William M. ..... Duluth
Spano, Joseph P. ..... Minneapolis
Speckhals, Robert C. ..... Faribault
Spencer, Bernard J. ..... Minneapolis
Spencer, David L. ..... Anoka
Spencer, Robert J. ..... Rochester
Sperl, Michael P., Jr. ..... St. Paul
Spiekerman, Ralph E. ..... Rochester
Spieler, F. B. ..... Pequot Lakes
Spink, Wesley W. ..... Minneapolis
Spittell, John A., Jr. ..... Rochester
Sponsel, Kenath H. ..... Minneapolis
Sporre, Knute A. ..... Fergus Falls
Sprafka, Gregory A. ..... St. Paul
Sprafka, Joseph L. ..... St. Paul
Sprague, Randall G. ..... Rochester
Spraitz, Anton F., Jr. ..... St. Paul
† Spring, Donald A. ..... Rochester
† Spurzem, Raymond J. ..... Anoka
† Stacey, Richard R. ..... Rochester
Stadem, Clifford ..... Crookston
Stafne, John G. ..... St. Paul
Stahl, George W. ..... Austin
Stahr, Aubrey C. ..... Hopkins
Stahler, Paul A. ..... Jordan
Stam, John ..... Worthington
† Stambuk, Berigoj K. ..... Rochester
† Stanford, Charles E. ..... Elcho, WI
† Stanley, Court R. ..... Minneapolis
† Starkey, Thomas A. ..... Rochester
Staub, Henry P. ..... Minneapolis
Stauffer, Maurice H. ..... Rochester
† Stauffer, Richard N. ..... Rochester
Stecker, Raymond H. ..... APO New York, NY
† Steffens, Leon A. ..... Red Wing
Steidl, Richard M. ..... Minneapolis
Stein, Raymond J. ..... Pierz
Stein, Robert L. ..... North St. Paul
Stein, William A. ..... Duluth
Steinberg, Charles L. ..... St. Paul
Steiner, Andrew M. ..... St. Michael
Steiner, Leon E. ..... Albert Lea
Steinhilber, Richard M. ..... Rochester
Stelter, Lloyd A. ..... Minneapolis
Stemsrud, Harold L. ..... Alexandria
Stengl, Thomas A. ..... St. Paul
Stenseth, Jon H. ..... APO New York, NY
† Stenstrom, Annette T. ..... Grand Marais
Stenzel, Donald A. ..... Minneapolis
Stenzel, Joseph A. ..... Minneapolis
Stephens, William E. ..... Minneapolis
† Sterling, Wm. A. ..... Rochester
Sterner, Donald C. ..... St. Paul
Sterner, Ernest R. ..... St. Paul
Sterner, John J. ..... St. Paul
Sterrie, Norman A. ..... Minneapolis
† Stevens, John C. ..... Rochester
Stewart, Donald E. ..... Crookston
Stewart, James R. ..... El Paso, TX
Stewart, Marvin J. ..... Minneapolis
Stewart, Paul B. ..... Minneapolis
Stickney, J. M. ..... Rochester
Stiegler, Farrell S. ..... Minneapolis
Stifter, Anton J. ..... Winsted
Stiles, Clifford D. ..... Foley
Stillwell, George K. ..... Rochester
Stillwell, Walter C. ..... Mankato
Stilwell, George G. ..... Rochester
Stobbe, Juergen A. ..... APO New York, NY
Stoesser, Albert V. ..... Minneapolis
Stoker, Lynn C. ..... Albert Lea
Stolee, Curtis N. ..... Ft. Dauphin, Madagascar
Stolee, Thomas A. ..... St. Paul
Stolen, Keith H. ..... Grand Rapids
Stoltz, Robert C. ..... Minneapolis
Stone, Norman F. ..... Minneapolis
Stone, Stanley P. ..... Minneapolis
Storsteen, Kenneth A. ..... Duluth
Stover, Laddie E. ..... Marshall
Stoy, Robert A. ..... Little Falls
Strait, Herbert S. ..... Minneapolis
Strand, Clarence M. ..... Minneapolis
Strand, Jack W. ..... Jasper
Stansky, Theodore W. ..... Owatonna
Strathern, Carleton S. ..... St. Peter
† Stratte, Alf K. ..... Pine City
† Stratte, Harold C. ..... Windom
Stratte, Jon R. ..... Stillwater
Strauchler, John ..... Belview
Straus, Maurice L. ..... St. Paul
Street, Bernard ..... Northfield
Streitz, John M. ..... Duluth
Strem, Edward L. ..... St. Paul
Streu, Richard E. ..... Minneapolis
Strewler, Gordon J. ..... Duluth
Strickland, Martha J. B. ..... St. Paul
Strickler, Jacob H. ..... Minneapolis
Strobel, Claire J. A. ..... Mankato
Strobel, Jack L. ..... Minneapolis
Stroebel, Charles F., Jr. ..... Rochester
Strom, Gordon W. ..... Minneapolis

Strom, Robert L. ..... Minneapolis
Stromgren, Delph T. ..... Minneapolis
Stromme, William B. ..... Minneapolis
Strong, Cameron G. ..... Rochester
Strunk, Clarence A. ..... Minneapolis
† Stubbs, Samuel E. ..... Rochester
Student, Richard E. ..... Minneapolis
Studer, Donald J. ..... Faribault
† Stuhr, John W. ..... Stillwater
Sturges, Robert L. ..... Minneapolis
Sturley, Rodney F. ..... St. Paul
Subak, Barbara H. ..... Minneapolis
Subby, Walter ..... Minneapolis
† Suiter, Ronald D. ..... Rochester
Sukov, Marvin ..... Minneapolis
Sulciner, Aurel ..... Minnetonka
Sullivan, W. Albert, Jr. ..... St. Paul
Summar, M. Thomas ..... Virginia
Summerskill, William H. ..... Rochester
Sundberg, A. Bruce ..... Minneapolis
Sutherland, John E. ..... Indian Head, MD
Svien, Hendrik J. ..... Rochester
Swaiman, Kenneth F. ..... Minneapolis
Swallen, Thomas O. ..... Minneapolis
† Swanson, David A. ..... Minneapolis
† Swanson, Gerald E. ..... St. Paul
Swanson, John O. ..... Minneapolis
Swanson, Lawrence J. ..... West St. Paul
Swanson, Ralph H. ..... West St. Paul
Swedberg, William A. ..... Duluth
Swedenburg, Paul A. ..... Glenwood
Sweetser, Horatio B. ..... Minneapolis
* Sweetser, Theodore H. ..... Minneapolis
Sweetser, Theodore H., Jr. ..... Minneapolis
Swendseen, Carl J. ..... Minneapolis
Swendson, James J. ..... St. Paul
Swensen, Don P. ..... Duluth
Swenson, Arnold O. ..... Duluth
Swenson, Donald B. ..... St. Paul
Swenson, Donald B. ..... Mankato
Swenson, Floyd J. ..... Grand Rapids
† Swenson, James D. ..... Edina
Swenson, Orvie J. ..... Waseca
Swenson, Richard W. ..... Minneapolis
Swenson, Roy G. ..... North Branch
Swift, Dean C. ..... Minneapolis
Symchych, Boris E. ..... Minneapolis
Symmonds, Richard E. ..... Rochester
Syverson, Leslie A. ..... Fergus Falls

T

† Tachovsky, Thomas J. ..... Rochester
Taintor, Ronald W. ..... Marshall
Tam, Ernest C. ..... Minneapolis
Tambornino, Joseph M. ..... Minneapolis
Tanaka, Shin ..... Minneapolis
Tanasichuk, Murray A. ..... St. Paul
† Tancredi, Robert G. ..... Rochester
Tangen, George V. ..... Minneapolis
Tani, George T. ..... St. Paul
† Tanquist, Edwin J. ..... Alexandria
Tanquist, Edwin J., Jr. ..... Alexandria
Taswell, Howard F. ..... Rochester
Tate, Wayne E. ..... South St. Paul
Taufic, Mansur ..... Austin
Tauxe, Welby N. ..... Rochester
† Taylor, Joseph H. ..... Ft. Lauderdale, FL
* Taylor, William E. ..... Minneapolis
Tchou, Mien-Fa ..... Minneapolis
† Teem, Martin V., Jr. ..... Rochester
Teeter, Richard R. ..... St. Paul
Teisberg, John E. ..... St. Paul
Teller, Richard M. ..... Albany, NY
Tenner, Robert J. ..... Minneapolis
Terrell, Bernard J. ..... Nopeming
Tesch, Gordon H. ..... Elk River
Teska, Byron A. ..... Minneapolis
Testor, James V. ..... Winona
Tetlie, James P. ..... Duluth
Textor, Jerome ..... Anoka
Teynor, Joseph W. ..... Minneapolis
Thayer, Ellsworth A. ..... Fairmont
Thelemann, Arthur R., Jr. ..... Minneapolis
Theobalt, Inge M. ..... Minneapolis
† Thielen, R. D. ..... New Brighton
Thiem, Chester E. ..... Mankato
Thienes, R. Lawrence ..... St. Cloud
Thomas, John V. ..... Duluth
Thomas, Juergen E. ..... Rochester
Thomas, William H. ..... Minnetonka
Thomasson, Robert D. ..... Minneapolis
Thomes, A. Boyd ..... Minneapolis
Thompson, A. Henry ..... St. Peter
Thompson, Arthur ..... Minneapolis
Thompson, Carl O. ..... Hendricks
Thompson, Dennis P. ..... China Lake, CA
Thompson, Gershom J. ..... Rochester
Thompson, James I. ..... Duluth
Thompson, James R. ..... Bemidji
Thompson, Russell A. ..... Willmar
† Thompson, Wayman J., Jr. ..... Rochester
Thompson, Wayne W. ..... St. Paul
† Thomson, James M. ..... Austin
Thorsgard, Ernest O. ..... Thief River Falls
Thorson, Stuart V. ..... Minneapolis
Thurber, Deloran L. ..... Rochester
Thurn, Roy J. ..... Duluth
Thysell, Desmond M. ..... Minneapolis
Thysell, Vernon D. ..... Moorhead
Tietz, Charles A. ..... Virginia
Tiffany, Francis B. ..... St. Paul
† Tiffany, Joseph C., II ..... Rochester
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Underdahl, Laurentius O. ..... Rochester
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V

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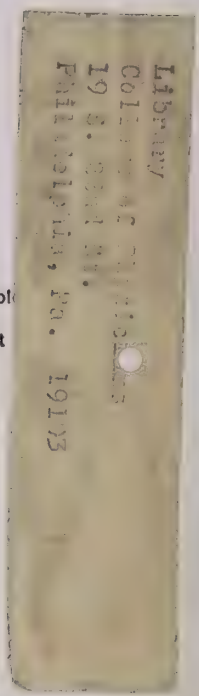


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Now, the same dependable antianxiety effect can be obtained with convenient tablets—Libritabs (chlordiazepoxide).





(in Libritabs™)
(chlordiazepoxide)

Before prescribing, please consult complete product information, a summary of which follows:

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

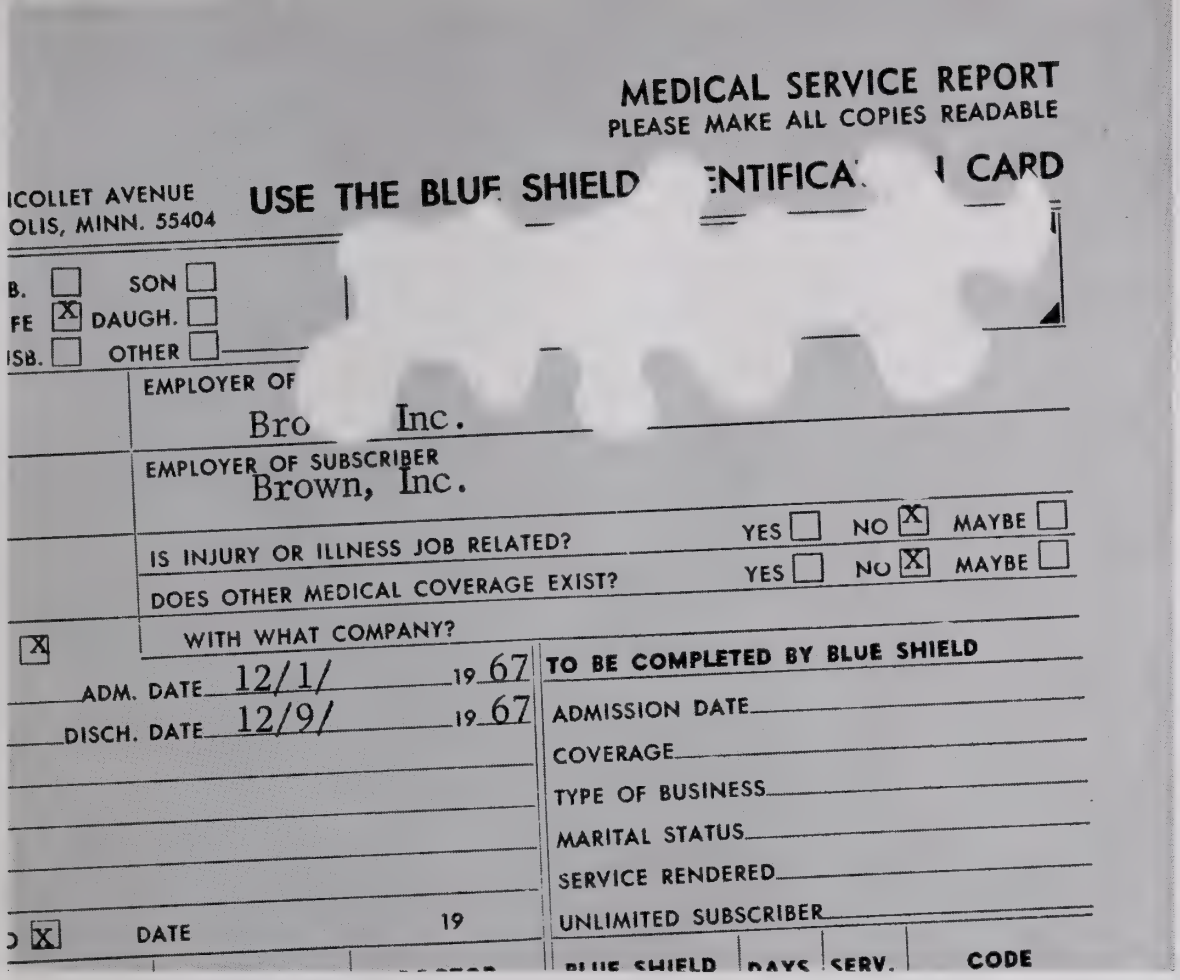
Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver-function tests advisable during protracted therapy.

Usual Daily Dosage: Individualize for maximum beneficial effects. *Oral*—Adults: Mild and moderate anxiety and tension, 5 or 10 mg t.i.d. or q.i.d.; severe states, 20 or 25 mg t.i.d. or q.i.d. Geriatric patients: 5 mg b.i.d. to q.i.d. (See Precautions.)

Supplied: Librium® (chlordiazepoxide HCl) Capsules, 5 mg, 10 mg and 25 mg—bottles of 50. Libritabs™ (chlordiazepoxide) Tablets, 5 mg, 10 mg and 25 mg—bottles of 100. With respect to clinical activity, capsules and tablets are indistinguishable.

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Open-eyed nights





Too tense to sleep...too tired to get up. **Early to bed, late to rise, and not much sleep at that, the patient with severe psychic tension is understandably tired. His tensions and overreactions to the day's stresses may interfere with proper sleep, and his inability to face the day's activities can produce an ever-worsening pattern. By relieving psychic tension, Valium® (diazepam) facilitates sleep, particularly with an h.s. dose. In many patients, the usefulness of Valium has been demonstrated in relieving psychic tension alone or with secondary depressive symptoms. Valium is generally well tolerated and, with proper maintenance dosage, usually does not unduly impair mental acuity or ability.**

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders; athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindications: Known hypersensitivity to drug; children under 6 months of age; acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in treatment of psychotic patients, and should not be employed in lieu of appropriate treatment. As with most CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increase in dosage of standard anticonvulsant medication; abrupt withdrawal in such cases may also be associated with temporary increase in frequency and/or severity of seizures. Advise patients against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance. Keep addiction-prone individuals (such as drug addicts or alcoholics) under careful surveillance because of their predisposition to habituation and dependence. Use of any drug in pregnancy, lactation or in women of childbearing age requires that potential benefit be weighed against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam), such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. Employ usual precautions in the severely depressed or in those with latent depression; suicidal tendencies may be present and protective measures necessary. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation (initially 2 to 2½ mg once or twice daily, increasing gradually as needed or tolerated).

Adverse Reactions: Side effects most commonly reported: drowsiness, fatigue and ataxia. Infrequently encountered: confusion, constipation, depression, diplopia, dysarthria, headache, hypotension, incontinence, jaundice, changes in libido, nausea, changes in salivation, skin rash, slurred speech, tremor, urinary retention, vertigo and blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued. Because of isolated reports of neutropenia and jaundice, periodic blood counts and liver function tests are advisable during long-term therapy. Minor changes in EEG patterns (low-voltage fast activity) observed during and after therapy and are of no known significance.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg; bottles of 50, 100 and 500.

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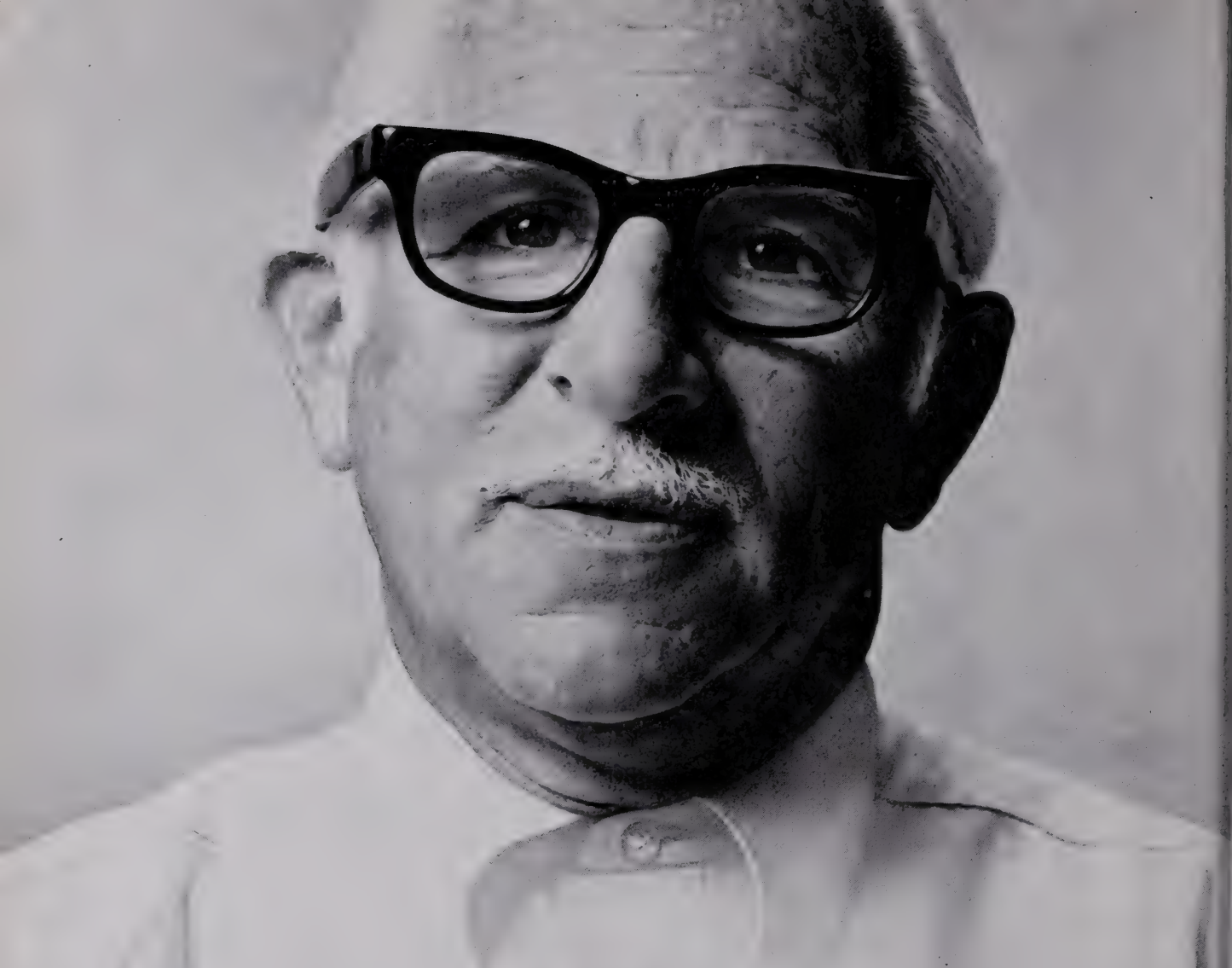
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Demethylchlortetracycline HCl 300 mg and Nystatin 500,000 units CAPSULE-SHAPED TABLETS Lederle

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To guard susceptible patients against intestinal monilial overgrowth during broad-spectrum therapy—the protection of nystatin is combined with demethylchlortetracycline in DECLOSTATIN.

For your susceptible candidates, prescribe DECLOSTATIN—the broad-spectrum therapy that prevents monilial overgrowth.

Contraindication: History of hypersensitivity to demethylchlortetracycline or nystatin.

Warning: In renal impairment, usual doses may lead to excessive accumulation and liver toxicity. Under such conditions, lower than usual doses are indicated, and, if therapy is prolonged, serum level determinations may be advisable. A photodynamic reaction to natural or artificial sunlight has been observed. Small amounts of drug and short exposure may produce an exaggerated sunburn reaction which may range from erythema to severe skin manifestations. In a smaller proportion, photoallergic reactions have been reported. Patients should avoid direct exposure to sunlight and discontinue drug at the first evidence of skin discomfort. Necessary subsequent courses of treatment with tetracyclines should be carefully observed.

Precautions: Overgrowth of nonsusceptible organisms may occur. Constant observation is essential. If new infections appear, appropriate measures should be taken.

In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment.

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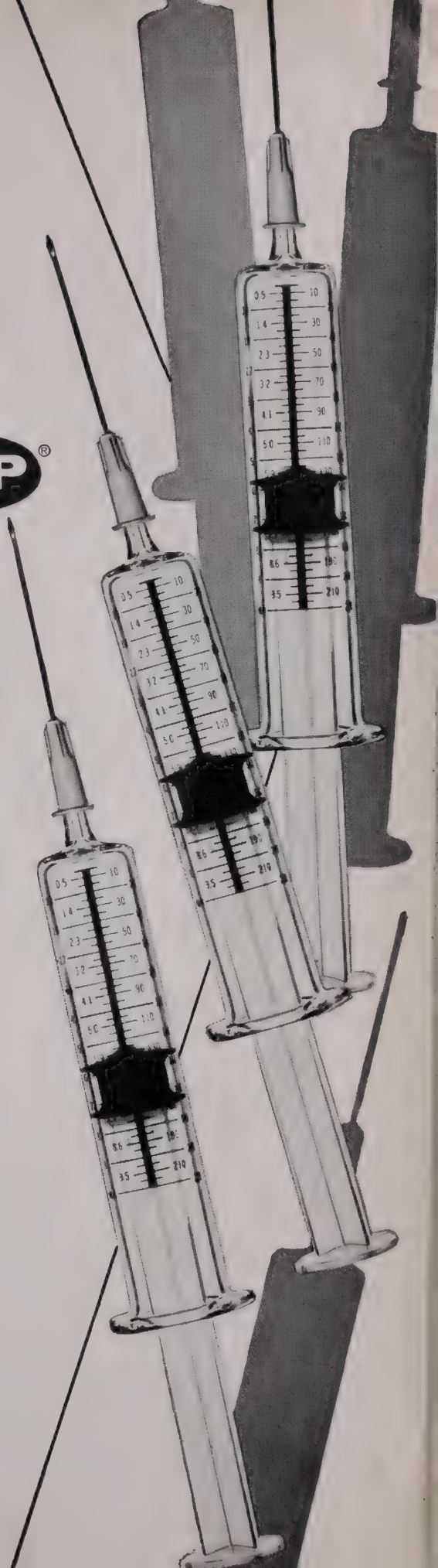
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President's Letter

Anesthesia in Minnesota

ATTENTION HAS BEEN focused in the past year on the practice of anesthesiology in the hospitals of Minnesota. What began as an inquiry into the qualifications of those administering general anesthetics has progressed to several active plans for continuing education of physicians and nurses. Standards and guidelines for anesthesia departments, to improve the quality and safety of anesthesia, should soon evolve.

Early in 1967 the Minnesota Society of Anesthesiologists submitted a resolution to the Minnesota State Medical Association requesting that it conduct such studies as were necessary to establish minimal standards of training and competence for persons administering anesthetics. The House of Delegates of the Minnesota State Medical Association passed the resolution and designated its Committee on Anesthesia to carry out the fact-finding survey. A complete survey of Minnesota hospitals was not needed because recent information was already available. The State Board of Health had done studies in 1958 and in 1966, in relation to licensing of hospitals, on the training qualifications of those giving anesthetics.

In brief, by 1966 there had been much improvement in the qualifications and training of those giving anesthetics. There are 432 certified registered nurse anesthetists employed in 172 of the 184 hospitals in Minnesota. There are approximately 140 trained anesthesiologists in the state. Two hospitals use only anesthesiologists, 112 have only certified registered nurse anesthetists, and 45 have both anesthesiologists and anesthetists. In the state are 20 smaller hospitals in which some anesthetics are not given by full-time physician-specialists or certified registered nurse anesthetists. In five of these, anesthetics are given by general practitioners; in four others, anesthetists are registered nurses with formal anesthesiology training but are not certified. Five hospitals use nurses with less than complete anesthetist training and six others use "job-trained" anesthetists. In all, seven persons with less than full nurse anesthetist training and 10 with job training are administering anesthetics.

The following recommendation was approved by the Minnesota State Medical Association in March 1968: That an Anesthesia Advisory Committee to the State Board of Health be formed, to draw up a voluntary set of standards and guidelines for departments of anesthesia in Minnesota. Representatives from the Minnesota State Medical Association, Minnesota Hospital Association, Minnesota Nurse Anesthetists' Association, and Minnesota Society of Anesthesiologists will be included. A cooperative endeavor by all these organizations to develop regional educational programs and equipment standards should do a great deal to improve safety in anesthesia.

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Mitral Valve Reconstruction

JOSEPH C. KISER, M.D.
THEODORE A. PETERSON, M.D.
FRANK E. JOHNSON, M.D.
Minneapolis, Minnesota

In spite of recent advances in prosthetic valve design and construction, arterial embolization and mechanical dysfunction continue to be serious problems. In the mitral position, the hazard of embolization seems to be particularly severe, even with optimal anticoagulant control.[1] Perhaps more consideration should be given to repair of the existing valve when conditions warrant. In the absence of calcification or extensive loss of tissue substance of the anterior mitral leaflet, application of proven repair techniques may yield satisfactory results.

The following five case reports are examples of severe mitral valve disease treated by various reconstruction techniques. In three of these patients, multiple valve disease was present. All five patients are living and have shown early evidence of improvement.

Case Reports

Case No. 1:

A 65-year-old female was a functional class III-c, moderately cachectic with known atrial fibrillation of ten years duration. Grade IV apical holosystolic murmur and grade II apical diastolic murmur. No ascites, hepatomegaly, or peripheral edema.

Chest X-ray and Cardiac Fluoroscopy

Cardiomegaly with double contour of left atrial enlargement, minimal mitral valve calcification.

Electrocardiogram

Atrial fibrillation, right axis deviation with ST and T-wave changes consistent with digitalis effect.

Cardiac Catheterization

Pulmonary artery pressure 60/25, wedge 35 (mean), cardiac output 1.5 L/min/m^2 (index). No aortic valve gradient. Aortic root injection revealed no aortic valve incompetence. Left ventricular injection demonstrated marked mitral regurgitation.

Surgery August 8, 1967

Heart enlarged in all chambers. Left atrium markedly enlarged. Strong thrill over the left atrium posteriorly. No thrill palpable over the right atrium. The patient's condition deteriorated with anesthesia, so that pressure measurements could not be obtained. Extracorporeal circulation was instituted and the mitral valve was exposed from the right side. There was some calcification at the posteromedial commissure and a fixed orifice measuring about 2.0 × 1.5 cm. The commissural fusion was split to the annulus in both directions. There was marked subvalvular fusion of the chordae tendinae.

The anterior papillary muscle was incised longitudinally between the chordae and a posteromedial annuloplasty was performed. There was no systolic thrill over the left atrium at the conclusion of the procedure.

The immediate postoperative condition was satisfactory without any tendency toward the "low output syndrome." Her convalescence was slow but uncomplicated. Fluid retention did not occur. She was discharged from the hospital on the twentieth postoperative day.

Case No. 2

A 52-year-old female was a functional class III with bilateral pleural effusions. Recent onset of atrial fibrillation. Grade IV systolic ejection murmur at the left sternal border, radiating into the base of the neck. Grade III holosystolic apical murmur radiating toward the axilla and audible in the back. Grade II blowing diastolic murmur heard along the left sternal border. No ascites, hepatomegaly or peripheral edema.

Chest X-ray and Cardiac Fluoroscopy

Cardiomegaly with evidence of left atrial enlargement. No valvular calcification seen.

Electrocardiogram

Atrial fibrillation, digitalis effect.

Cardiac Catheterization

Confirmed the clinical diagnosis of severe aortic valve disease and marked mitral valve incompetence.

Surgery September 6, 1967

Heart enlarged in all chambers. No thrill over the right atrium and no definite thrill over the left atrium. The aortic valve was found to be severely diseased and was replaced with a #3 Cutter prosthesis. The mitral valve was predominantly stenotic with a central orifice measuring 7 to 8 mm. in diameter. There was minimal calcification in the posteromedial commissure. The commissures were split to the annulus in both directions and a posteromedial annuloplasty was performed. The remainder of the procedure was concluded in a routine fashion.

The postoperative course was uncomplicated. At the time of dismissal from the hospital, there was a grade I apical systolic murmur.

Case No. 3

A 36-year-old female with recurrent mitral stenosis had had a closed mitral commissurotomy performed eight years prior to this admission. Functional class II-b with increasing dyspnea on exertion in the past year and hemoptysis two months prior to this admission. Loud apical diastolic rumble with an opening snap audible.

Chest X-ray and Cardiac Fluoroscopy

Mitral configuration. No evidence of valvular calcification.

Electrocardiogram

Sinus rhythm, right axis deviation.

Surgery January 17, 1968

Dense adhesions obliterating the pericardial space. Moderately enlarged left atrium. Diastolic thrill palpable over the left ventricle. No systolic thrill palpable over the left atrium. Extracorporeal circulation was instituted and the mitral valve was exposed from the right side. The valve was severely stenotic with a central orifice that measured about 7 mm. in diameter. There was no valvular calcification. The dilator was introduced and with the first attempt, the anterolateral commissure opened completely, but a severe rent occurred posteriorly and medially. This commissure was then incised with a knife and a posteromedial annuloplasty performed. At the conclusion, the diastolic thrill was gone and there was no systolic thrill palpable over the left atrium.

The postoperative course was uncomplicated and there were no murmurs audible at the time of dismissal from the hospital.

Case No. 4

A 71-year-old female, functional class IV, had had rheumatic fever at age 15 years with symptoms of dyspnea on exertion being prominent at age 55 years. She had taken digitalis for fifteen years. Progressively more severe dyspnea during the past four years and currently dyspneic at rest. Marked neck vein distention in the sitting position. Previous history suggestive of ascites. Grade IV holosystolic murmur at the apex, radiating to the axilla and audible in the back. Grade III systolic murmur along the lower right sternal border which seemed louder with inspiration. Liver enlarged and pulsatile. No ascites or peripheral edema evident.

Chest X-ray and Cardiac Fluoroscopy

Marked enlargement of all chambers with considerable enlargement of the right atrium. No valvular calcification seen.

Electrocardiogram

Atrial fibrillation.

Cardiac Catheterization

Confirmed the clinical diagnosis of severe mitral incompetence and ruled out aortic valve disease. Right atrial pressure 18/8 Hg with activity of the catheter in the right ventricle suggesting marked tricuspid incompetence. Severe pulmonary hypertension with a pulmonary artery pressure of 110/38. Unable to obtain a wedge pressure.

Surgery March 14, 1968

All chambers enlarged with marked enlargement of the right atrium. Strong thrill palpable over the right atrium and posteriorly over the left atrium. Unable to obtain pressure measurements. Extracorporeal circulation was established and the mitral valve was exposed from the right side. There was minimal calcification in the commissures near the annulus. There was a fixed central orifice measuring approximately 2.0 × 1.0 cm. Both commissures were split to the annulus. There seemed to be adequate substance to the anterior leaflet, although the edge was rolled and there was moderate chordal thickening and fusion. A posteromedial annuloplasty was performed. The tricuspid valve was examined through a separate incision in the right atrium. There did not appear to be organic disease present. A tricuspid annuloplasty was performed by placing figure-of-eight stitches in the annulus between the anterior and septal leaflets. At the conclusion of the procedure, there was no palpable thrill over the left atrium, although there remained a thrill over the right atrium.

Her convalescence was prolonged, but without specific

complication. At the time of discharge, twenty-two days after surgery, there remained a prominent systolic murmur heard over much of the precordium, but not radiating to the axilla or to the back.

Case No. 5

A 58-year-old male, functional class III with progressive deterioration in the past two years, was admitted in congestive heart failure. With appropriate diuretics, his weight dropped from 162 pounds to 147 pounds. Marked cardiomegaly with a hyperactive apical impulse in the seventh left interspace at the anterior axillary line. Grade V apical holosystolic murmur and a harsh grade IV systolic murmur in the aortic area. Soft grade II diastolic blowing along the left sternal border. Liver slightly enlarged. No peripheral edema or ascites evident.

Chest X-ray and Cardiac Fluoroscopy

Marked cardiomegaly with evidence of left atrial enlargement, moderate calcification in aortic and mitral valve region.

Electrocardiogram

Sinus rhythm, left ventricular hypertrophy.

Cardiac Catheterization

Confirmed the clinical findings of severe mitral incompetence and marked aortic stenosis and incompetence.

Surgery March 21, 1968

Heart markedly enlarged in all chambers. Strong systolic thrill over the left atrium posteriorly and a moderate systolic and diastolic thrill over the aortic root. Right atrial pressure 10-12, left atrial pressure 28-30. Right ventricular pressure 30/2, left ventricular pressure 75/4, aortic pressure 75/25. Extracorporeal circulation was instituted and coronary perfusion was maintained throughout the procedure. The mitral valve was exposed from the right and found to contain only minimal calcification. The posteromedial commissure was partially fused and there were several ruptured chordae along the posterior leaflet. Both commissures were completely opened by sharp dissection. The ruptured chordae were repaired and a posteromedial annuloplasty was performed. The aortic valve was replaced with a #4 Cutter prosthesis.

His postoperative course was complicated by a right hemothorax requiring thoracentesis. He was dismissed on the seventeenth postoperative day. There was a grade II systolic murmur at the apex at the time of discharge which has since diminished.

Discussion

Mitral valve reconstruction was widely employed in the early days of open heart surgery. More recently, the major emphasis has been on valve replacement with prostheses of varying design and composition. In spite of the predictable hemodynamic results that can be anticipated with these prostheses, major problems still need to be overcome. Reported mortality rate figures for mitral valve replacement still are in the range of 14%-20% with the "low output syndrome" accounting for a large percentage of these deaths. Accumulated data[1] indicates that perhaps as many as 50% of patients may experience systemic embolism within thirty-six months after mitral valve replacement with the standard Starr-Edwards prosthesis. Although the early reports with cloth-covered valves have been enthusiastic, the effectiveness of this innovation is yet to be proved. Valve ring detachment from the mitral annulus, ball variance, and bacterial endocarditis also occur.

Mitral valve reconstruction in many instances can produce satisfactory results. In the absence of heavy calcification or deficient tissue in the anterior leaflet, reconstruction may be preferable to replacement. Reliable techniques that can be employed include sharp division of commissural fusion, posteromedial annuloplasty, repair of ruptured chordae, direct suture of tears or perforations, and mobilization of subvalvular fused chordae by longitudinal incision of the papillary muscles. The hemodynamic improvement gained may be difficult to assess at the time of surgery, but one may be fairly certain that significant improvement has been obtained if the systolic thrill of incompetence over the left atrium is abolished. Rarely is the murmur of mitral insufficiency completely eliminated by these techniques. However, with time, the murmur does not often increase in intensity.

Patients who have had successful mitral valve reconstruction do not require postoperative anticoagulation routinely, and systemic embolism is uncommon. Uncertain as we are regarding the etiology of the "low output syndrome," it does not often accompany mitral valve reconstruction. Recognizing the relatively rare incidence of this latter complication after mitral valve reconstruction, one might anticipate significant reduction in the operative mortality for mitral valve disease if the patients are properly selected and the techniques appropriately applied.

Our group of patients is small in number and the followup is short. There was one postoperative complication—a hemothorax requiring aspiration. Three of these mitral reconstructions were performed on patients under-

going surgery for multiple valve disease. Those patients who required concomitant aortic valve replacement have been maintained on anticoagulants. The "low output syndrome" did not occur and none of them required assisted ventilation during the postoperative period. Three of these five patients have a residual apical systolic murmur. There were no operative deaths.

Summary

1. In the absence of heavy calcification or severely deficient valve substance in the anterior leaflet, mitral valve reconstruction can provide satisfactory results.

2. The risk of postoperative arterial embolism is reduced.

3. This procedure can be accomplished with low operative mortality.

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President's Letter **(Continued from Page 893)**

The Minnesota Society of Anesthesiologists believes that, while the other organizations are necessary to the success of the effort, it must assume the primary responsibility and leadership in the attempt to ensure good anesthesiology practice in this state. The fact is that there will not be an anesthesiologist at the head of every operating table in the foreseeable future. Thus, it behooves us to be teaching, helping, and even being responsible for those who are giving anesthetics. Our Society has an enthusiastic Committee on Education, with Dr. Van S. Lawrence as chairman. They are working on continuing education at the anesthetist level, with good cooperation from the Department of Health and the Nurse Anesthetists' Association. Our Society has a Speakers Bureau, with Doctors J. J. Buckley and J. T. Martin as chairmen. They offer to provide speakers on anesthesiology and related subjects to any county society or hospital staff, without cost.

These are our aims and activities; we invite your ideas and ask your cooperation for their success.

Emerson A. Moffitt, M.D.
President
Minnesota Society of Anesthesiologists

Abdominal Muscle Deficiency Syndrome

This syndrome consists of (1) partial or complete absence of abdominal musculature; (2) hydroureter, hydronephrosis, and megabladder; (3) undescended testes in males; and (4) malrotation of the intestine. Fröhlich described the first case in 1839. Fifty-eight cases have been reported to date (Mathieu *et al.*), only four of which were females.

Deficiency or absence of the abdominal muscles includes the lateral groups, the transversus, and the obliques. The recti are often present. Symptoms more often pertain to the genitourinary tract or to one of the other numerous congenital abnormalities. These include pigeon breast deformity, spina bifida with myelomeningocele, hydrocephalus, congenital bladder neck obstruction, bilateral hydroureter, urachus,* and perhaps talipes. The clinical course is often complicated by episodes of infections that require antibiotics and possible surgery. Many of these patients have a low intelligence quotient and require chronic institutional care.

*See Test Your Word Score Page 937.

It may be true that the willing horse gets the heaviest load. But once in a while he also gets the most oats.—Forbes Epigrams

The Marinesco-Sjögren Syndrome*

Hereditary Cerebello-Lental Degeneration with Mental Retardation

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A FAMILIAL SYNDROME characterized by cerebellar ataxia, cataracts, and mental retardation was described in 1931 by Marinesco et al.[1] Subsequently, Sjögren[2] showed that the disorder is inherited as a recessive trait. In 1962 a review[3] of the literature disclosed less than forty published cases. We have recently encountered an additional case and have had an opportunity to reevaluate the variety of clinical and pathological features found in this disorder. We were able to document an abnormality of skeletal muscle. The rarity of the syndrome prompted us to report our observations.

Case Report

A nineteen-year-old boy was admitted to the University of Minnesota Hospitals for evaluation of an unsteadiness which made walking extremely difficult. He had been born after a full-term pregnancy and had weighed eight pounds at birth. Although delivery required forceps, there were no neonatal complications and the infant appeared healthy.

Retarded Rate of Development

By four to five months of age, it was recognized that his rate of development was slow. He appeared weak and did not hold up his head well. He was a year old before he reached for objects. By two years of age, he began to feed himself. Although he was toilet-trained and could say some words by two years, he did not stand alone until three years of age. He was not able to walk until age twelve. Prior to this, he moved about by inching along on his buttocks. After age twelve, he could walk if assisted. He was nineteen years old before he could walk without support, but even then his gait was unsteady.

Bilateral cataracts were removed at age three. Speech was never clear. Intelligence was estimated to be at the upper end of the defective range, and he had to attend special classes in school. His disposition was pleasant and he posed no behavioral problems.

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Fig. 1—Note residual cataract, protuberant ears, and underdeveloped mandible. (Patient's permission given to reproduce figure.)



Fig. 2—The patient has a thin, lanky build, full breasts, normal phallus and pes planus. Muscle development is poor.

Family History

The patient's mother and an older sister were healthy. The father had had a successful resection of a bronchogenic carcinoma, but he died of a cerebrovascular accident at age 65. Both parents were of Norwegian descent but denied any consanguinity.* The maternal grandmother had cataracts in old age. The family history failed to suggest visual disturbances, weakness, unsteadiness, muscle wasting, baldness, stiff muscles, endocrine disturbance, or mental retardation in other members.

General Examination

The patient (Figures 1, 2, and 3) was cooperative and pleasant when first examined by the authors in 1964. His height was 5 feet, 6 inches (1.65 meters), and his skull circumference 21 inches (53.3 cm). His hair was normal. His breasts were rather large but true gynecomastia was not present. Abnormalities included prominent ears, a recessed mandible, long neck, high arched palate, absent upper right lateral incisor, absent left optic lens, residual cataract on the right, and "pigeon breast" deformity of the sternum. The heart, lungs, and abdomen were normal. The pubic hair showed a female configuration. The testes were small and soft. The phallus was normal. Other skeletal anomalies were a lumbar lordosis, a wide-flared pelvis, bilateral pes planus with short third, fourth and fifth toes, incurved third toe and short fifth fingers of both hands.

Dermal Pattern

Dermatoglyphic analysis showed ulnar loops on nine fingers. A radial loop was present on the left middle finger, an unusual site for this pattern. The total finger ridge count was a low 58. The atd angles, interdigital patterns, hypothenar, thenar, hallucal and great toe patterns were unremarkable. The palmar crease pattern was normal. Dermatoglyphics have not previously been reported in the Marinesco-Sjögren syndrome; consequently it is not known whether a low finger ridge count and an unusually placed radial loop are characteristic of this disorder.

Neurological Findings

Examination of cranial nerves showed intact olfaction.* Visual fields and the left optic fundus were normal; the right fundus could not be visualized. There was some limitation of ocular movement on lateral gaze and on convergence, but movements were conjugate.* Fine horizontal nystagmus was noted on lateral gaze and, occasionally, vertical nystagmus was elicited. The left pupil was slightly larger than the right; both pupils reacted normally to light. There was slight weakness of the masseter and temporalis muscles and their bulk was decreased bilaterally. Slight weakness of facial muscles was evidenced by the inability to close the eyelids tightly. Hearing was good. There was marked dysarthria, the speech resembling that of a young child who substitutes sounds and abbreviates syllables. The voice had an explosive quality. The tongue protruded in the midline,

*See Test Your Word Score Page 937.

but rapid alternating side-to-side and front-to-back movements of the tongue were not well performed.

Motor strength and bulk were decreased in all extremities, more proximally than distally. The grip was also weak. There was no evidence of myotonic phenomena. Fasciculations were not seen. The tendon reflexes were difficult to elicit but symmetrical. Abdominal reflexes were absent bilaterally. The Babinski response could not be elicited. A sucking response was present.

Coordination was markedly impaired. A gross intention tremor was elicited on finger-to-nose and heel-to-knee testing. He sat with minimal difficulty, but was unable to stand without support. The gait was wide-based and staggering. Balance while standing with eyes closed or open was equally poor. Sensation was normal.

Laboratory Data

The hemogram and urinalysis were normal. Results of other laboratory tests were: negative Kline test, blood urea nitrogen 14 units, calcium 9.2 mg. percent, phosphorus 4.0 mg. percent, two-hour fasting blood sugar 67 mg. percent, alkaline phosphatase 9 King-Armstrong units, serum lactic acid dehydrogenase 366 I.U., creatine phosphokinase 18.9 units (normal is 1 to 11 units), protein-bound iodine 5.9 μg percent, 17-ketosteroids 11.7 and 17-hydrosteroids 6.4 mg. both per 24 hours, serum creatine 0.6 mg. percent and urine creatine 0.91 gm. both per 24 hours, and standard creatinine clearance 170 gm. per 24 hours. Amino acid chromatography revealed an alpha-amino nitrogen excretion of 202 mg. per 900 cc. which is at the upper limit of normal. However, the relative excretion of alanine was moderately decreased.

X-Ray Changes

A roentgenogram of the skull was normal. The mandible was small in relation to the facial bones. An overbite was evident. Spine x-rays showed asymmetrical development of the body of C5, and juvenile epiphysitis involved T4 through T10 with resultant dorsal kyphosis. The medial end of the clavicles had an abnormal shape. Several ribs had a spindle-like appearance. The superior and inferior rami of the symphysis pubis were tapered. The tibiae showed slight depression of the medial plateau and both fibulae had a spindle shape. Hand x-rays were interpreted as normal, but the feet showed incurving of the third metatarsal and shortening of the fourth metatarsal bones bilaterally.

Nerve Conduction and Electromyography

Because of the poor muscle development, electrodiagnostic studies were obtained. These demonstrated normal motor conduction velocities for the right median (53 meters per second), right ulnar (57 meters per second) and right peroneal nerves (53 meters per second).

Concentric needle electrode examination of proximal and distal muscles of all extremities revealed normal insertion and resting potentials except in the left tibialis anterior where occasional fibrillation potentials firing at a low frequency were observed.



Fig. 3—Side view showing long neck, tendency to carry head forward, lumbar lordosis and poor muscle bulk.



Fig. 4—The pes planus and shortened third, fourth and fifth toes are evident.

During voluntary contraction, most motor unit action potentials were of low voltage (100-200 mv), polyphasic, and of normal duration. A few were of very short duration (1-2 msec.). The electromyogram was interpreted as being indicative of a myopathic process.

Muscle biopsies were obtained from the right biceps and left anterior tibial muscles, both of which showed a greater than normal variation in fiber size plus increased endomyseal fibrosis and fat. The muscle was considered to be abnormal but the findings were not specific. Electron microscopic studies of this muscle by Dr. E. Benson showed no abnormalities.

Discussion

Since the literature on this disorder was reviewed in 1962,[3] several additional case reports of the Marinesco-Sjögren syndrome have been published, and some reports not included in that review have been found. This new material is summarized below.

Characteristic Case Histories

Moravczik's[4] three patients had ataxia, nystagmus, dysarthria, cataracts, pes equinovarus, and retarded somatic and psychic development characteristic of hereditary cerebello-lental degeneration. However, he did not consider his cases to be examples of a unique entity but rather a variant of Friedreich's ataxia.

Müller[5] described a mentally retarded male reared in an orphanage. Nothing was known about the family. Cataracts were observed at nine months. Strabismus, horizonal nystagmus, ataxia of limbs and trunk, hypotonia, absent tendon reflexes, and a normal toe response to plantar stimulation were also found. A second male apparently unrelated to the first was also described. He too had retardation of mental and physical development and was still unable to stand alone at six years of age. The following signs were noted: bilateral cataracts, ataxia, poorly enunciated speech, nystagmus, hyporeflexia, hypotonia, Babinski on the left, hypogenitalism, genu valgum,* and pes valgus.

Norwood[6] described two cases. The first was a white male who was small at birth, who had retarded mental and physical development, and whose head circumference at two years of age was 17½ inches. Cataracts, strabismus, nystagmus, ataxia, poorly developed muscles with normal tone, normal reflexes, and kyphosis were noted. The hair was depigmented and of the lanugo type.

A female, unrelated to the first patient, showed the same ocular, neurological and skeletal features described in the first patient. Her hair was also depigmented and showed no definite medulla. The hair anomaly had not previously been noted in the Marinesco-Sjögren syndrome. Chromosomal studies in the two patients were normal.

Máttyus et al.[7] described two additional cases. A male adolescent had dysarthria, limb ataxia, coerulear cataracts, hyperreflexia but no Babinski response, spasticity and mental retardation (IQ 61); the circumference of the skull and muscle development were normal. No skeletal deformities were mentioned. He was less than five feet tall.

Their second case was the younger brother of the first patient. He too was retarded mentally (IQ 65). His height was 141 cm. and there was a pes planus. The skull was normal. Cryptorchidism was found and corrected with hormonal therapy. He was ataxic and dysarthric but there was no nystagmus. Cataracts were present. He showed twisting movements of the head. Tendon reflexes were exaggerated and a tendency to a Babinski response was found on one side.

Cases Differing from True Syndrome

The cases described by Géraud et al.[8] under the label of the Marinesco-Sjögren syndrome are, in our opinion, erroneously classified. Bilateral cataracts, cerebellar ataxia, and pes cavus were present; but there were many dissimilarities when compared with other examples of the Marinesco-Sjögren syndrome. The features reported which are not seen in the Marinesco-Sjögren syndrome include an onset of neurological disability and mental deficiency in middle life and sensory deficits. Moreover, the mother of the patients was similarly affected, suggesting dominant rather than recessive inheritance.

A brother and sister thought to have the Marinesco-Sjögren syndrome were described by Zlatoverov and colleagues.[9] However, unlike cases with this syndrome, the boy showed normal development until one year of age, but thereafter there was progressive impairment of both physical and mental growth. Ataxia of gait developed, and by age seven, he had difficulty standing. The corneas were clouded (cataracts?). He died after an unsuccessful

*See Test Your Word Score Page 937.

attempt to perform pneumoencephalography. The post-mortem examination showed evidence of toxoplasmosis, hypoplasia of internal organs, adherence of pericardium to epicardium, increased connective tissue, thickened and opacified meninges, and cystic degeneration of the cerebral cortex. The brain was more firm than normal when sectioned, and the ventricles were dilated. Histological examination showed pyknotic cells with indistinct Nissl substance. Glial proliferation was present. Areas of old necrosis were seen in the region of the dentate nucleus, the third ventricle, and the infundibulum. Perivascular calcifications were present. The sister had a similar rapid course but was not as well described clinically. The rapidly progressive course and normal development in infancy is unlike what has been described in other cases of Marinesco-Sjögren syndrome. This diagnostic label is probably not appropriate for Zlatoverov's cases.

Crome and his colleagues[10] described siblings with congenital cataracts and neurological abnormalities due to unknown cause and included the Marinesco-Sjögren syndrome in the differential diagnosis. However, cerebellar ataxia was not a prominent feature. Renal abnormalities and seizures which were present are not characteristic of the Marinesco-Sjögren syndrome. In our opinion, the clinical picture in Crome's cases is therefore distinct from that shown by the patients with genuine Marinesco-Sjögren syndrome.

Nick et al.[11] described a male with cataracts, cerebellar ataxia, and mental aberrations. He also had extrapyramidal features and seizures. They considered him to be an example of the Marinesco-Sjögren syndrome. However, the cataracts developed in adolescence, the ataxia became manifest at age 35, and the intellectual deficit was not apparent until middle life. In addition, there was a family history of cataracts. Therefore, although there were several features in common with the Marinesco-Sjögren syndrome, the dissimilarities are sufficiently striking to warrant exclusion of this case.

Francois[12] reviewed a number of disorders in which congenital cataracts were seen. None of the disorders, however, included ataxia as a prominent feature and it should not be difficult to distinguish them clinically from the true Marinesco-Sjögren syndrome. In his discussion, Francois accepts the possibility that the spino-cerebellar ataxia of Marinesco-Sjögren syndrome may be replaced by muscular atrophy and cites the report of Dufour et al.[13] as supporting evidence. We hold that cerebellar ataxia is one of the most important features of the Marinesco-Sjögren syndrome; we do concede, however, that muscle wasting and poor muscle development is another feature shown by some affected individuals.

Mild Muscle Disorder

The poor muscle development in our case was noteworthy. The clinical examination, electromyogram, muscle biopsy and slightly elevated creatine phosphokinase were all compatible with the existence of a mild, probably chronic, myopathy. Muscle abnormalities have been mentioned in other cases with this syndrome[2,3] and may be a common feature. The muscle disorder, however, is mild and contributes less to the patient's disability, at least initially, than the cerebellar dysfunction. That the muscle disorder may also be slowly progressive is suggested by Sjögren's long-term followup evaluation of some of his cases. In the family reported by Alter et al.,[3] the degree of muscle wasting was greatest in the oldest affected individual and least in the youngest.

Prominent Features

On reviewing cases reported with hereditary cerebello-lental degeneration, three clinical features emerge as major signs, while others are more variable and may be considered as minor signs. The first major feature includes *cerebellar ataxia.* The ataxia is always present in infancy and results in a marked delay in development of motor skill, such as sitting and walking. The affected individual eventually compensates for this deficit and is able to ambulate. However, walking may be delayed until puberty and is never performed with facility. There is a suggestion that walking ability may again be lost, possibly as a result of progressive muscle weakness rather than ataxia. Dysarthric speech having a child-like quality and nystagmus are also characteristic. Other types of extra-ocular movement disorders are also present but may represent nuclear rather than internuclear defects of innervation. Strabismus is very commonly present.

A second major feature is *cataract*. The type of cataract, however, shows considerable variability.[3] There is some question as to whether the cataract is always congenital, but there is general agreement that it begins very early in life and by three to five years of age is sufficiently severe to reduce visual acuity markedly. Early treatment of the cataract represents the one therapeutic measure available in this disorder which offers much hope of improvement to the patient.

A third major feature is *mental and physical retardation*. The mental retardation is of mild to moderate degree and not progressive. The individual can be trained to carry out simple tasks and manage his personal hygiene quite well. Physical retardation is also of mild degree but is regularly present. The affected individuals have short stature. Our patient was 1.65 meters tall and is one of the taller patients described.

Less Common Features

The clinical features which are common but not invariably present include *skeletal anomalies* of variable nature. Short and misshapen digits on the hands or feet, microcephaly, dental anomalies, kyphosis, rib anomalies, and vertebral body defects, among others, have been described.

Pyramidal tract involvement is present in about half the cases, as evidenced by spasticity and a Babinski response.

Sensory defects are *not* present. The tendon reflexes in some cases are absent, as in Friedreich's ataxia. *Muscle involvement* has not been investigated in any detail, but none of the previously reported cases were robust of build. Studies in our patient suggest that there may actually be a mild myopathic component to the syndrome. The hair anomaly reported by Norwood[6] has not been recognized by other observers.

Genetic Considerations

Inheritance follows a recessive pattern. Consequently, consanguinity of the parents is likely and should specifically be asked about whenever an affected individual is encountered. The fact that cases have now been reported from many widely separated parts of the globe suggests that the gene locus responsible for the syndrome may mutate with a fair frequency. It is doubtful that carriers of the recessive trait disseminated it so widely in different populations, but this possibility cannot be excluded. As expected in single gene disorders, chromosomal studies[6,14] have been negative.

The pathology of the disorder in the nervous system remains to be elucidated. Details available are meager and are based on brain biopsy material or on cases whose classification is open to question.

The biochemical basis of the disorder remains as genetically obscure today as when the syndrome was first described.

Summary

A sporadic case of hereditary cerebellolental degeneration with mental retardation (Marinesco-Sjögren syndrome) has been described, and a myopathic component has been documented for the first time with electrodiagnostic techniques and muscle biopsy. The literature on this rare syndrome has been critically reviewed. Major signs include cerebellar ataxia, cataracts, and mental and physical retardation. Minor signs include strabismus, dysarthria and nystagmus, probably related to the cerebellar involvement; skeletal anomalies including kyphosis, microcephaly, deformities of ribs, hands, and feet; pyramidal signs; and mild myopathy. The syndrome is inherited as an autosomal recessive disorder. The pathology of the brain and the underlying biochemical defect are still unknown.

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If you are trying to kill time, always make sure it is your own.—Herbert Prochnow

Placental Localization

The Use of Technetium^{99m} Albumin and the Scintillation Camera*

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THE CLINICAL management of the pregnant subject who has had third trimester vaginal bleeding is simplified if the location of the placenta can be ascertained. Prior to the general availability of short-lived radioisotopes such as technetium^{99m}, attempts were made to localize the placenta using radioactive pharmaceuticals such as I^{131} serum albumin or chromium^{51}-labelled red cells.[1] Considerable effort was then spent on locating the placenta by counting several areas of the abdomen individually. Because of the rather long physical and biological half-life of these preparations, the amount of radioisotope administered was necessarily small, so that the radiation exposure to the patient and the fetus might be maintained within acceptable limits. This small amount of radioactivity precluded the use of conventional scintiphotographic procedures which provide pictorial presentations of the placenta and hence better overall accuracy in placental localization than is possible with spot counting.

In an earlier communication reference was made to the use of technetium-labelled albumin and a scintillation‡ camera for several diagnostic procedures.[2] Among these procedures was localization of the placenta in a manner initially described by McAfee and associates.[3] Since that time several reports of placental localization with technetium-labelled albumin have appeared in the literature.[4,5,6,7]

The purpose of this report is three-fold, first, to review our experience using technetium^{99m}-labelled, albumin in 51 pregnant subjects, secondly, to report on the scintillation (Anger) camera for the localization of the placenta, and finally to study the fetal transfer of radioactivity and thereby assess the radiation hazard of the procedure.

*Supported in part by funds from the Graduate School, University of Minnesota.

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With technical assistance of Stephen Bostrom, R.T.

‡See Test Your Word Score Page 937.

Principles and Methods

Technetium^{99m} has a physical half-life of six hours and is obtained from a Mo^{99}-Tc^{99m} generator* by saline elution. Technetium^{99m} decays without beta emission to its ground state, giving off a 140 Kev gamma photon. This photon is nearly ideal for use with the scintillation camera, particularly with a low-energy multichannel collimator now available for use with this instrument.

Technetium^{99m}-labelled albumin is prepared daily in our laboratories. The method is modified after the technique of Stern and associates[8] and requires approximately one hour to complete. Consistent yields of greater than 80 per cent technetium-labelled albumin have been obtained. The small amount of technetium which remains unlabelled is removed by passage of the albumin mixture through a resin column (Dowex-50*). The material is then sterilized by passage through a millipore filter. Aliquots are taken daily for sterility evaluation. Placental scintiphotograms are obtained immediateley after the intravenous administration of 0.5 to 2 millicuries of the labelled albumin. One to two minutes of time was required for each scintiphotogram to be obtained with the scintillation camera.

Results

All of the subjects studied had a digital localization of the placenta performed at the time of delivery. After completion of the delivery a comparison of the two results was made. Excellent correlation was obtained in all but one patient where insufficient numbers of scintiphotograms were obtained in various projections in order to determine whether or not the placenta was located on the anterior or posterior wall of the uterus.

Position of Placenta

Two patients in our series were found to have a central placenta previa and another subject had a marginal placenta previa. In each instance the correct diagnosis was made from the scintiphotograms. Scintiphotograms from the remaining group of patients showed the placenta to be located away from the internal os of the cervix; in all cases this was verified by subsequent digital examination.

Figure 1 shows a scintiphotogram obtained

*E. R. Squibb and Company.

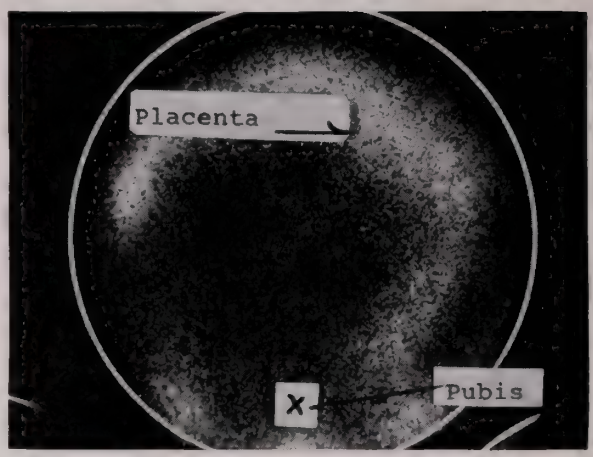


Fig. 1—Scintiphotogram of the anterior projection of the abdomen showing a complete placenta previa.

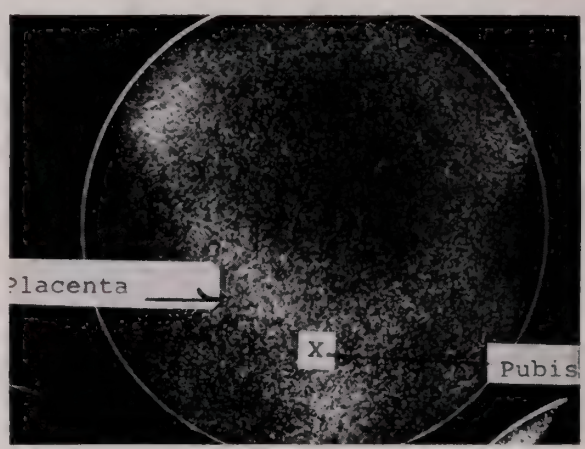


Fig. 2—Scintiphotogram of a marginal placenta previa.

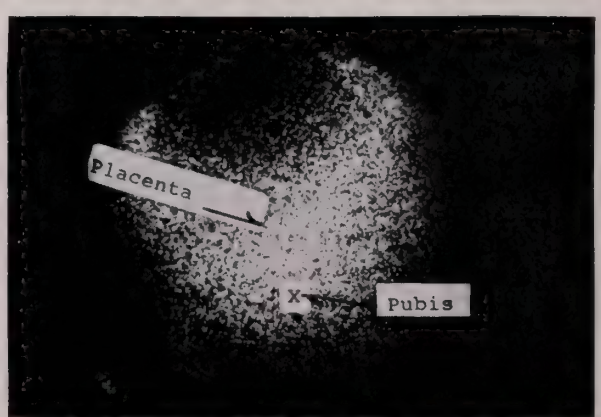


Fig. 3—Scintiphotogram of the anterior abdominal wall showing the placenta in a normal location near the dome of the uterus. Note the radioactivity in blood vessels in the iliac regions and in the uterine wall.

following the administration of one millicurie of technetium^{99m} albumin intravenously. The scintillation camera was directed toward the anterior aspect of the abdomen. The placenta is located near the dome of the uterus to the left of midline. Figures 2 and 3 show scintophotograms from two other patients obtained in a manner similar to that used for the study shown in Figure 1. Figure 2 shows a marginal placenta previa. Figure 3 shows a complete placenta previa.

Radioactivity of the Blood

In ten subjects venous blood was serially obtained for two hours following technetium^{99m} albumin administration and also at the time of delivery. Whenever possible, umbilical cord blood and amniotic fluid were also obtained. These data are summarized in the Table. External counts were made on two of the infants following delivery within three hours of the time of maternal administration of the radioisotope. *In no case was there significant radioactivity found in the infants.*

Discussion

The management of a pregnant subject who is bleeding per vagina is a complex and hazardous problem for the obstetrician. These results together with those published by other investigators indicate that placental localization by the scintiphotographic technique following the administration of technetium^{99m} albumin is a useful diagnostic tool in evaluating this problem. In all of our patients, the placenta was visualized adequately, and in all but one case it was located correctly in the uterus. Three of our patients were found by the scintiphotograms to have placenta previa and all were delivered by cesarean section.

Placental Barrier

Our data indicate that essentially no radioactivity crosses the placental barrier since we did not find any significant radioactivity in the infants following delivery. In one infant, cord blood was found to show some radioactivity (17 per cent of maternal blood counts per cc) which indicates that in this particular study not all of the administered technetium was labelled to the albumin. Thus the removal of any "free" technetium from the labelled albumin preparation prior to its use for placental localization is desirable. However, some clinics are advocating the use of the pertechnetate ion (no albumin label) because of the relatively small radiation dose involved.[9]

Minimal Radiation Dose

The radiation dose to the mother and the fetus appears to be well within acceptable limits. The radiation is considerably below that which would be received by conventional radiographic techniques for evaluation of the placental location. The maternal radiation exposure following administration of one millicurie of technetium-labelled albumin has been estimated by Smith to be 50 millirads to the blood and 3-6 millirads to the total body.[10] Because of the very low transport of this radioisotopic preparation across the placental wall, the fetal dose will be approximately the same as the total body maternal dose (3-6 millirads).

False Results

No false positive or negative results of pla-

TABLE I
Fetal Transfer of Radioactivity

Patient	Maternal Specimens (Blood)* Time After Injection 1 hour	2 hour	3 hour	At Delivery	Time of Delivery After Injection	Fetal Specimens† Cord Blood	Amniotic Fluid
J.M.	100%	83%	....	105%	50 min.	17	2
T.B.	100	84	76	74	3.7 hrs.	5	....
J.W.	100	85	84	60	5 hrs.	7.1	....
B.T.	100	78	69	0	5 days	0	....
C.D.	100	84	57	100	1 hr.	3.2	....
K.K.	100	84	....	84	2 hr.	5.3	....
M.W.	100	86	75	75	3.1 hr.	6.1	1.7
A.N.	100	74	64	92	1.3 hr.	3.8	....
C.I.	100	73	52	73	2 hrs.	4.5	1.3
B.H.	100	90	85	0	14 days	0	0

*Based on per cent of maternal blood counts per cc at one hour post-injection.
†Based on per cent of maternal blood counts per cc at time of delivery.

centa previa were found in our series. Nonetheless, both results are possibilities and should be watched; for, if there is heavy vaginal bleeding, the pooled vaginal blood which contains radioactivity may give falsely positive scans. A false-positive might also result from excessive technetium in the bladder. This can, of course, be eliminated as a source of error by frequent voiding during the sequential scintiphotograms. A false-negative scan could be obtained in the rare presence of a succinate lobe of the placenta.

Value of Knowing

The final decision as to the obstetrical management in placenta previa depends upon the amount of placenta which overlies the inverval os of the cervix. At the present time this can be determined only by a digital examination prior to delivery. If possible all suspected cases of placenta previa are managed conservatively prior to 36 weeks of gestation in order to avoid the delivery of a premature infant. This can be expensive and inconvenient for both the physician and the patient. One very useful purpose of the placental scan is therefore the safe elimination of most vaginal bleeding cases from this high-risk suspect group, because the placenta will usually be shown to lie away from the lower uterine segment. This information will also encourage the physician to think of the other causes for bleeding in those cases. It will also make the conservative management more intense and cautious in those cases where the placenta is low in the uterus. These latter cases will ultimately come to the operating room for a double-set-up vaginal examination which will then reveal the exact location of the placenta and thus the mode of delivery for that patient.

Summary

The use of technetium^{99m} and the scintillation camera afford a reliable and atraumatic way for determining placental location in the pregnant subject. The radiation exposure to both mother and fetus is exceedingly low (3-6 millirads). The scintillation camera permits several scintiphotograms of the maternal abdomen to be obtained in a short time, usually in less than a half hour.

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Blockheads of Different Degrees

I hold that there is every variety of natural capacity, from the idiot to Newton and Shakespeare; the mass of mankind, midway between these extremes, being blockheads of different degrees: education leaving them pretty nearly as it found them, with this single difference, that it gives a fixed direction to their stupidity, a sort of incurable wry-neck to the thing they call understanding. So one nose points always east, another always west, and each is ready to swear that it points due north.—Thomas Peacock

Happiness may be thought, sought or caught, but not bought.—Mutual Moments

Sulfobromophthalein Sodium

Fatal Reactions

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DANIEL H. GREGORY, M.D.*
Minneapolis, Minnesota

SULFOBROMOPHTHALEIN has been widely accepted in evaluation of hepatic function since its clinical application was initially recognized in 1925.[1] Only after 23 years of extensive use was the first non-fatal adverse reaction to sulfobromophthalein dye described, and no fatalities were reported until 1956.[2,3]

Iber listed 14 fatal and 18 non-fatal reactions.[4] He noted that all reactions to sulfobromophthalein are not recognized as such, and of those recognized, not all are reported. Thus the number of reported fatalities represents only a minimal estimation of the incidence. Wang and Jacobson reviewed the literature in 1966 and noted that there were 19 cases with complications, eight of which had been fatal.[5] They reported an additional three cases of adverse reactions without fatality. Their review showed that half of those patients with fatal reactions and one third of those with non-fatal reactions had had previous exposure to sulfobromophthalein. A positive history of allergic sensitivity was noted in 40% of the fatal cases.

The subject of this review is to remind the physician of the potential danger of this diagnostic drug and to include two additional cases of fatality associated with the administration of sulfobromophthalein.

Case Reports

Case 1

A 55-year-old white male farmer entered the Minneapolis Veterans Hospital with a cough productive of yellow sputum, shortness of breath and increasing fatigability. During the previous 11 years, he had experienced progressive shortness of breath and intermittent wheezing attacks that were relieved by bronchodilators. Two years prior to admission he was hospitalized with fever, malaise and chills. Chest x-rays had demonstrated bilateral apical infiltrates. A diagnosis of eosinophilic granuloma was established by lung biopsy. After a three-week course of prednisone (initial dose 60 mgm; then gradually tapered), there was some roentgenographic clearing of the apical infiltrates associated with subjective clinical improvement. Subsequently, however, his

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clinical course deteriorated and finally resulted in the present admission.

Abnormal findings on admission, including hepatomegaly, prolongation of the prothrombin time (15 seconds; control 12.5 seconds) and an alkaline phosphatase of 19.8 KAU/100 ml, indicated the need for a sulfobromophthalein test. After injection of 2-3 ml of sulfobromophthalein dye, it was apparent that extravasation had occurred and the procedure was terminated. The attending physician left the room for approximately two minutes. Upon his return the patient was cyanotic, apneic and without a discernible heart beat. Resuscitation efforts were initiated witthin five minutes of the sulfobromophthalein administration and included endotracheal intubation, intravenous and intracardiac epinephrine (1.0 ml of 1:1000) and external cardiac massage. These efforts were unsuccessful.

The postmortem findings showed emphysema, pulmonary fibrosis and histiocytosis. Neither acute bronchial constriction nor laryngeal edema was present. The cause of death was considered to be an anaphylactoid reaction associated with the administration of sulfobromophthalein dye.

Case 2

A 37-year-old white male was admitted to the Minneapolis Veterans Hospital following an episode of infectious hepatitis. After clinical recovery he underwent a sulfobromophthalein retention test without untoward side effects. Three days prior to hospitalization, a repeat sulfobromophthalein test had been performed by his private physician. Immediately following the injection of dye, the patient had developed a severe anaphylactoid reaction and within one hour underwent cardiac arrest. He was successfully resuscitated and immediately hospitalized locally, where anisocoria*, hypotension and bilateral Babinski reflexes were noted.

On the day of admission to the hospital, his temperature rose to 105°, followed by another cardiac arrest. After resuscitation, he required vasopressors, corticosteroids, antibiotics and a tracheostomy. His blood pressure became unresponsive to medical therapy, and he expired the day after admission.

Discussion

Although a cause and effect relationship between sulfobromophthalein and the fatal outcome in these cases cannot be definitely established, it is clear that both patients suffered acute anaphylactoid reactions after the administration of sulfobromophthalein dye. Various adverse reactions have been noted after its use: chills, headache, fever, urticaria, generalized dermatitis, injection discomfort, venous induration at the injection site and serious anaphylactoid reactions.

Mateer et al., in a review of liver function tests, reported that such minor symptoms as chills, headaches and faintness were occasionally seen after the administration of sulfobromophthalein.[6] Stempien and Rosenquist reported that thrombophlebitis occurred in the injected vein in 0.6% of patients receiving sulfobromophthalein injections.[7]

Incidence

To date, 14 fatal and 18 non-fatal reactions to sulfobromophthalein have been recorded in the literature. An allergic history was recorded in 14 of these cases. Three patients had positive allergic histories and two others had asthma. In one case there was a family history of asthma. In the remaining cases, there was neither a personal nor a family history of allergy.

In at least eight of the cases previously reported, including three fatal reactions, there was no clear history of receiving sulfobromophthalein prior to the injection that caused anaphylaxis. Nine cases were known to have had previous tests without adverse effects, even though in two of these there had been extravasation of dye on previous tests.

The use of sulfobromophthalein dye is contraindicated in patients with an allergic or asthmatic history. Case 1 had an 11-year history of intermittent wheezing and a documented, antecedent allergic reaction. The administration of sulfobromophthalein dye to this patient was complicated by extravasation and resulted in a fatal outcome.

In Case 2 there was an apparent anaphylactoid reaction following the injection of sulfobromophthalein dye in a patient who had previously received the dye without adverse effect. Apparently, significant central nervous system damage had occurred before vigorous attempts at therapy were possible.

Contraindication

From the previously reported adverse reactions to sulfobromophthalein,[4,5,8] certain factors appear responsible and should be considered prior to the administration of the dye. These include: (1) a complete allergic history should be obtained from the patient; (2) patients who have previously experienced adverse reactions to sulfobromophthalein should not receive repeat tests; (3) observable extravasation of the injected dye into the extravascular

*See Test Your Word Score Page 937.

tissue should terminate the injection; and (4) tests for sulfobromophthalein retention should not be carried out without specific indications. In a patient with a previously demonstrated thrombophlebitis or an allergic reaction to the extravasated dye, extreme care should be taken if another test is indicated.[9]

Precautions to be taken during administration of the dye include: (1) administration should be done by a person who is prepared to deal with an acute anaphylactoid reaction; (2) the patient should be observed during the administration of the dye and at least five minutes afterwards; (3) the dye should be administered slowly over a period of five minutes; (4) extravasation of the dye should be avoided, and when observed should terminate the administration; and (5) vigorous resuscitation should be attempted in the event of an anaphylactoid reaction, for in a significant percentage of patients with adverse reactions to sulfobromophthalein, such efforts have been successful.[4,8]

Summary

During the 40 years that sulfobromophthalein sodium dye has been used as a test of hepatic function, there have been very few serious adverse reactions recorded in the literature. To date, 32 anaphylactoid reactions, including 14 with fatal outcome, have been reported. Continued reporting of serious or fatal adverse reactions to sulfobromophthalein should constantly alert the physician to the potential dangers of this frequently used test.

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"Make-Do" On the Frontier

A horse kicked a Klamath Falls, Oregon, ranch boy in the head and fractured his skull. Dr. John Patterson, called to the unconscious child's bedside, knew he had to relieve the pressure on his brain by removing a piece of bone, but he did not own a trephine, the cylindrical saw that surgeons use in this delicate operation. The doctor was undismayed. His frontier medical practice had accustomed him to "making do."

He took a thimble from the mother's sewing basket, sawed off the closed end, and filed teeth into the cut edge. Then he nailed the thimble to the end of a duster handle with a shingle nail. Cutting off the head of the nail, he filed it to a point so that he could center the instrument on the section of the boy's head he had to incise. Unlike many western doctors, Dr. Patterson had heard of the importance of sterilization, and he boiled his contraption in bichloride of mercury before setting to work. His patient recovered.*

*Richard Dunlop, M.D.: Doctors of the American Frontier.

Second Look Love

I am not one who do not believe in love at first sight, but I believe in taking a second look.—Henry Vincent

Medical Age Control

A certain Moscow polyclinic specializes along very unusual lines. The people who come there on certain days of the week hardly qualify as patients requiring medical aid. They have no complaints: neither of ailments and pains, nor of weakness and prostration. They are perfectly healthy and fit, and work at various institutions in different, sometimes highly important, capacities.

At the polyclinic they are regularly examined, investigated by the latest exacting methods, and advised on their mode of life, on how to work, how and what to eat, and how to rest. If symptoms of a disease, unsuspected by the patients, are discovered at the examinations, they are treated on the spot or sent to a clinic.

All these people have only one thing in common—their age. They are all past fifty, *all on in years, all on the threshold of old age.**

The doctors examine them, and those whose organs and tissues already show changes that are as yet slight and harmless but may turn into dangerous debilities if allowed to develop, are treated with the aim of arresting the process. This refers to persons with disorders such as high blood pressure, sclerosis of the connective tissue, thickening of the blood vessels, or atherosclerosis.

The doctors at the polyclinic are called upon to detect the incipient stages of these and similar debilities as early as possible. The visitors are given precise instructions on how to arrest the development of morbid changes. Persons with early symptoms of a disease are told how they must work and rest, and how to eliminate all harmful influences from their environment at work and at home. Regular examinations permit the doctors to control the loyal execution of all their therapeutic and preventive measures.

This is the first step of a remarkable undertaking aimed at turning the old age of people whose organisms already show signs of time's destructive action, into an unclouded and industrious period of their lives.†

*Editor's Note: Italics are mine.

†L. Fridland, M.D.: The Achievement of Soviet Medicine, Edited and translated by W. Horsley Gantt, M.D., 1961.

John Hunter—Lecturer

Lecturing was always an unpleasant task to Hunter who never lost his fear of addressing a class. He would brace himself each time by taking thirty drops of laudanum before facing the large audiences who came to hear his ideas on embryology, physiology, "animal chemistry," properties of matter, and the "life of the blood." The lectures took a great deal of his time and energy to prepare, since each was illustrated with materials from his unique museum, and he was continually revising and adding to his notes in the light of new observations. "You had better not write down that observation, for very likely I shall think differently next year," he would say to a prodigious note-taker. To one student who pointed out that he had just contradicted a statement of the year before, he replied: "Very likely I did; I hope I grow wiser every year."*

*Sarah R. Riedman: Masters of the Scalpel, 1962.

Someone has advanced the theory that the best way to break a habit is to drop it.—D. C. Yoder

Mediastinoscopic Diagnosis of Sarcoidosis*

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Sarcoidosis, a disease of unknown etiology, may involve multiple sites in various organ systems. Many areas are available for purposes of diagnostic biopsy. Obviously, the simplest biopsy procedure yielding histologically positive material is the procedure of choice. In suspected cutaneous and oral sarcoidosis, the preferred biopsy sites are the skin and mucosa, skeletal muscle biopsy when there are muscle symptoms, liver biopsy when the liver is enlarged or there are signs and symptoms of liver dysfunction, and biopsy of palpable nodes, e.g., epitrochlear.

Exceptions

However, a large number of affected patients do not qualify for the above procedures. These patients may have respiratory symptoms which prompt further evaluation, or they may have radiographic pulmonary abnormalities which are discovered fortuitously. For these patients there are several alternatives:

1. The clinical diagnosis of sarcoidosis may be made without histologic proof and the patient can be followed periodically for evolution or resolution of his disease. This course may be defensible when classic bilateral hilar adenopathy is present. However, many patients with suspected sarcoidosis may actually harbor an entirely different or additional disease process. If this is true, delay may be harmful to the patient.
2. The intradermal Kviem test for sarcoidosis can be given. Although reliable when a good antigen is available, this test usually requires about six weeks before a positive diagnosis by biopsy of the test site can be obtained.
3. Endoscopic procedures with biopsy and/or scalene node biopsy may be done.
4. An alternative is mediastinoscopy and biopsy of the hilar or paratracheal lymph nodes.

The purpose of this paper is to report our

*Presented at the Minnesota Academy of Ophthalmology and Otolaryngology Meeting, December 8, 1967.

experience using mediastinoscopy in the diagnosis of sarcoidosis.

Study Group

In the first 100 mediastinoscopies, the basic technique of Carlens[1,2] was followed with the exception of 51 cases which were done under local rather than general anesthesia. Knowledge of the anatomy is mandatory to avoid injury to major vessels and nerves.

Procedure

A transverse suprasternal notch incision approximately 4 cm. in length is made, and dissection carried down through the last layer of pretracheal fascia. Finger dissection is continued inferiorly, after which the mediastinoscope, an instrument resembling a laryngoscope, is introduced. Further dissection is done with a velvet-eye sucker tip.

A search for lymph nodes is made anteriorly, paratracheally, and along the main stem bronchus at and below the carina. The area of contemplated biopsy must be aspirated first with a long needle to avoid vascular injury and hemorrhage.

In active sarcoidosis the nodes are characteristically large and plump with a bluish violet color (Figure 1). In chronic long-standing disease the nodes are small, firm and grey in color. Once the tissue has been obtained the area is inspected for bleeding. If proper precautions are taken this should be negligible.

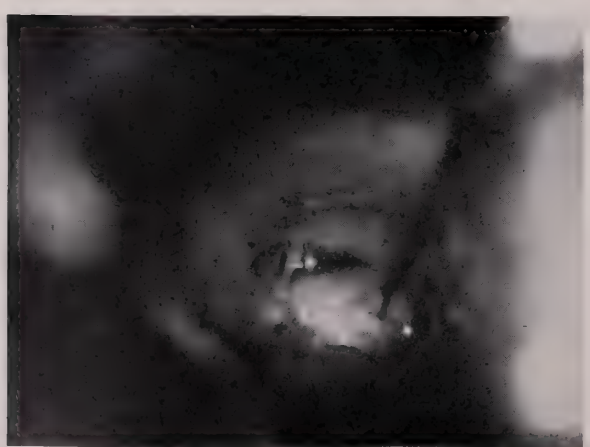


Fig. 1—View through the mediastinoscope. Large subcarinal sarcoid node being needled prior to biopsy. This node was not visualized by mediastinal planigraphy. Note pulmonary artery in upper right.

The incision is then closed snugly in layers.

Results

A diagnosis of sarcoidosis was made histologically in 16 of 100 patients having mediastinoscopy. Table 1 demonstrates that the radiographic picture is by no means stereotyped.

In five patients non-diagnostic bronchoscopy, including bronchial biopsies, preceded mediastinoscopy. In three patients scalene node biopsy was non-diagnostic. To our knowledge, no patient having a negative mediastinoscopy has subsequently been found to have sarcoidosis.

Discussion

The application of mediastinoscopy has grown considerably in recent years as accumulated data continues to support its safety and versatility. In our first 100 procedures, complications in the patients consisted of a left recurrent nerve paralysis in two individuals with extensive intrathoracic neoplasms, and one minimal pneumothorax which resolved without treatment. There have been no deaths. Postoperative antibiotics are no longer used. There has been no instance of mediastinitis, although a temperature spike often follows the procedure.

The results of thousands of mediastinoscopies have been reported in the world literature. The complication rate of our series parallels that of other large medical centers.[3,4] The mortality rate attributable to this procedure should be nil. We also feel the morbidity is less than that associated with scalene node biopsy.[5,6]

Effectiveness

The outstanding merit of mediastinoscopy

TABLE 1

Radiologic Picture on 16 Patients Found to Have Sarcoidosis at Mediastinoscopy

Reading	No. of Patients
Bilateral hilar adenopathy	9
Unilateral hilar adenopathy	2
Mediastinal widening	2
Diffuse pulmonary infiltrate with hilar adenopathy	1
Diffuse pulmonary infiltrate both upper lobes	1
Pericardial mass	1
Total	16

TABLE 2*
Sarcoidosis
Results of Diagnostic Procedures

Author	Bronchoscopy		Daniels Op.		Mediastinoscopy	
	No. Pts.	Positive	No. Pts.	Positive	No. Pts.	Positive
Fridel et al.	86	10.5%			30	100%
Lofgren et al.			47	32%	34	94%
Maassen	52	35%	26	62%	59	100%
Bergh et al.					33	100%
Carlens	56	20%			123	96%

*Carlens, E.: Mediastinoscopy. Ann. Otool. 74:1102, 1965.

is its very high diagnostic yield. Comparison studies from other centers substantiate this[7-10] (Table 2). Since the chest lesion is usually of undetermined etiology, mediastinoscopy may also provide histologic evidence of other disease processes, e.g., carcinoma, lymphoma, benign cysts, histoplasmosis, etc. In these instances patients are spared thoracotomy not only for certain benign lesions but also for malignant lesions which have extended beyond the confines of resectability.[11]

Bronchoscopy

Bronchoscopy, although not comparing favorably in terms of percent yield, does afford the opportunity of inspecting the endobronchial tree which may host not only the granuloma of sarcoidosis but other lesions as well. We feel that bronchoscopy should precede mediastinoscopy except in young people with no respiratory symptoms and classic x-ray findings. Both procedures can easily be accomplished at the same sitting.

Summary

In 100 mediastinoscopies sixteen cases of sarcoidosis were diagnosed. Three of these patients had negative scalene node biopsies and five had negative bronchoscopies and bronchial biopsies. None of the patients with negative mediastinoscopies have been found subsequently to have sarcoidosis. In this series there was minimal morbidity and no mortality. We believe that in the absence of palpable supraclavicular nodes, mediastinoscopy deserves priority over scalene node biopsy because of its higher diagnostic yield and safety.

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The people who find prosperity just around the corner—usually know which corner to turn.—Roster

Celestial Bed

James Graham: Quack

Graham was a remarkable quack: one of the early electrotherapists. The properties of electricity had only just become known and queues of patients waited at his rooms for the privilege of sitting on his "magnetic throne" or lying in an "electric bath."

The door of his Temple was always open, so that the poor might enter as freely as the rich. All that was demanded of the poor was a fee of six guineas. Once this formality was over, rich and poor males were alike conducted to the Great Apollo Apartment. Here the high priest himself lectured every day. Soft music always preceded his discourse, and at appropriate moments his audience received mild electrical shocks from the carefully wired chairs in which they were seated. As a grand finale an enormous spectre came up through the floor and handed to Graham bottles of his famous "aetherial balsam," guaranteed to promote all sorts of things.

Graham never had as many adherents for his mud-baths and open windows as were attracted by his electrical nonsense and the "aetherial balsam" which guaranteed fertility. If, despite the guarantee, the aetherial balsam did not promote a successful conception and lead to the production of the loveliest possible children, Graham placed at the disposal of his clients his wonder of wonders, the innermost mystery of the Temple of Health. This was his Celestial Bed, which was guaranteed to cure sterility.

The bed was in the centre of a spacious room pervaded always by rich scents and perfumes, and in which could be heard soft music from a string orchestra in an adjoining room. It was supported on six massive glass pillars and bedecked with blue satin. The slightest movement of the occupants made it oscillate rhythmically, and there ran through it electrical currents varying in intensity with the movements of the bed. This magnificent device was at the disposal of any lady and gentleman, preferably married. The price for one night in the bed, with breakfast, was fifty guineas. Graham said, in his Lecture on the Generation, Increase, and Improvement of the Human Species, published in London in 1784:

"Superior ecstasy which the parties enjoy in the Celestial bed is really astonishing and never before thought of in this world; the barren certainly must become fruitful when they are so powerfully agitated in the delights of love."

Graham was a shrewd investor and he reaped enormous dividends. Anyone who had not slept in the Bed was regarded by the world of fashion with the gravest suspicion. This vogue lasted for three most profitable years, at the end of which Graham returned to his native Edinburgh, there to preach the virtues of his mud bath. In his declining years he became first religious and later maniacal. He died suddenly in 1794.*

*Harvey Graham: A Doctor's London, 1952.

Esther B. Clark, M.D.

Doctor Esther B. Clark is a native born Californian who has practiced pediatrics in Palo Alto for 40 years. She has been the Head of the Department of Pediatrics of the Palo Alto Clinic since 1927. A member of the American Physicians Art Association, she has won many awards including a gold medal.

The picture on the cover, "California Foothills", was taken on Kodacolor film of a scene near some property she owns in Mendicino County, 200 miles north of Palo Alto.



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This high rate of cure obtained with Flagyl is unparalleled. Only systemically active Flagyl reaches the hidden reservoirs of reinfection in male and female genitourinary tracts.

Indications: Flagyl is indicated only in the treatment of trichomoniasis in both the male and female.

Contraindications: Pregnancy; disease of the central nervous system; evidence or history of blood dyscrasia.

Precaution: Complete blood cell counts should be made before, during and after therapy, especially if a second course is necessary.

Side effects: Infrequent and minor side effects include nausea, metallic taste and furry tongue. Gastrointestinal disturbances, flushing and headache sometimes occur, especially with concomitant ingestion of alcohol. The taste of alcoholic beverages may be altered. Other effects, all reported in an incidence of less than 1 per cent, are diarrhea, dizziness, vaginal dryness and burning, dry mouth, rash, urticaria, gastritis, drowsiness, insomnia, pruritus, sore tongue, darkened urine, anorexia, vomiting, epigastric distress, dysuria, depression, vertigo, incoordination, ataxia, abdominal cramping, constipation, stomatitis, numbness or paresthesia of an extremity, joint pains, confusion, irritability, weakness, cystitis, pelvic pressure, dyspareunia, fever, polyuria, incontinence, decreased libido, nasal congestion, proctitis and pyuria. Elimination of trichomonads may aggravate candidiasis.

Dosage and Administration: In women: one 250-mg. oral tablet three times daily for ten days. A vaginal insert of 500 mg. is available for local therapy when desired. When used, one vaginal insert should be placed high in the vaginal vault each day for ten days; concurrently two oral tablets should be taken daily.

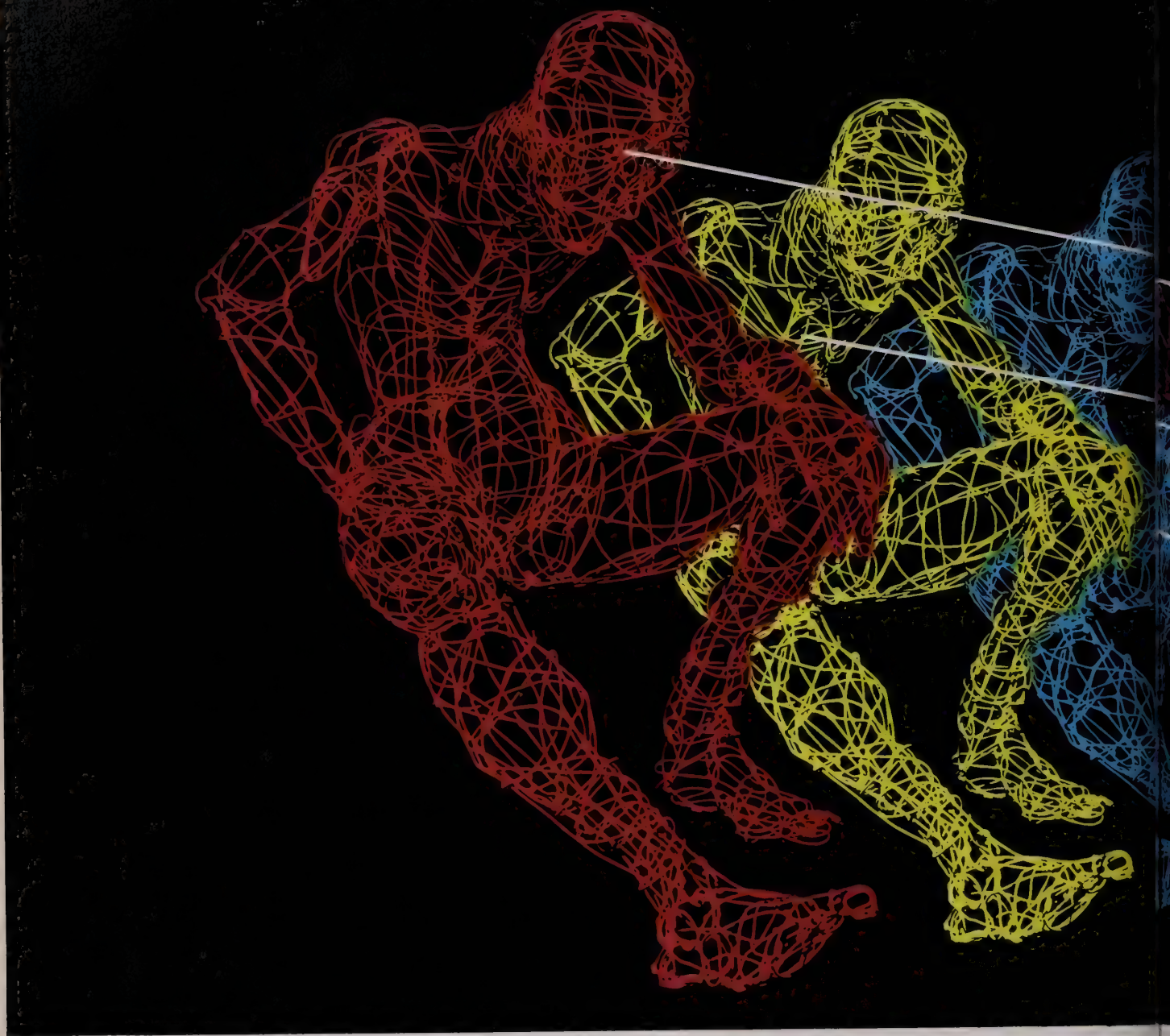
In men: When trichomonads are demonstrated, one 250-mg. oral tablet twice daily for ten days in conjunction with treatment of his female partner.

Dosage Forms: Oral tablets—250 mg.
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SEARLE

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Description: Each Pulvule® contains—

Special Liver-Stomach Concentrate, Lilly (containing Intrinsic Factor)	150	mg.
Cobalamin Concentrate, N.F., equivalent to Cobalamin (The total vitamin B_{12} activity in the Special Liver-Stomach Concentrate, Lilly, and the Cobalamin Concentrate, N.F., is 15 micrograms.)	7.5	mcg.
Iron, Elemental (as Ferrous Fumarate)	110	mg.
Ascorbic Acid (Vitamin C)	75	mg.
Folic Acid	1	mg.

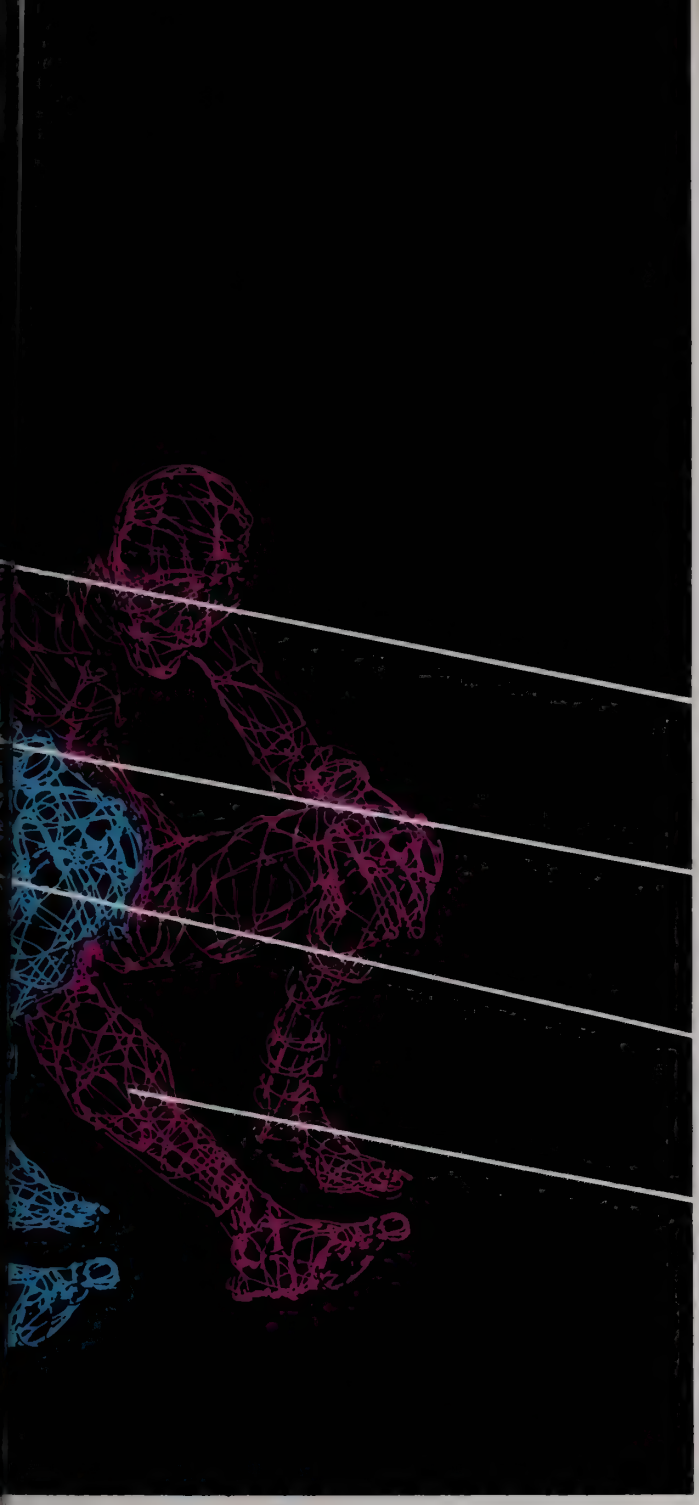
Indications: Trinsicon® (hematinic concentrate with intrinsic factor, Lilly) is a multifactor preparation effective in the treatment of anemias that respond to oral hematinics, including pernicious anemia and other megaloblastic anemias and also iron-deficiency anemia.

Contraindications: Hemochromatosis and hemosiderosis.

Precautions: Anemia is a manifestation that requires appropriate investigation to determine its cause or causes.

In pernicious anemia, the use of folic acid without adequate vitamin B_{12} therapy may result in hematologic remission but neurological progression. Adequate doses of vitamin B_{12} (parenteral, or oral with potent intrinsic factor as in Trinsicon® [hematinic concentrate with intrinsic factor, Lilly]) usually prevent, halt, or improve the neurological changes.

As with all preparations containing intrinsic factor, resistance may develop in some cases of pernicious anemia to the potentiation of absorption of physiological doses of vitamin B_{12}. If resistance occurs, parenteral therapy, or oral therapy with so-called massive doses of vitamin B_{12}, may be necessary. No single regimen fits all cases, and the status of the patient observed in follow-up is the final criterion for adequacy of therapy. Periodic



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Vitamin B_{12} plus intrinsic factor (15 mcg. B_{12} activity)—helps provide adequate levels of this important vitamin.

Folic acid (1 mg.)—treats nutritional macrocytic anemias and/or malabsorption syndromes.

Ascorbic acid (75 mg.)—augments the conversion of folic acid to its active form and helps iron absorption.

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clinical and laboratory studies are considered essential and are recommended.

Adverse Reactions: In rare instances, iron in therapeutic doses produces gastro-intestinal reactions, such as diarrhea or constipation. Reducing the dose and administering it with meals will minimize these effects.

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Dosage: One Pulvule twice a day. (Two Pulvules daily produce a standard response in the average uncomplicated case of pernicious anemia.)

How Supplied: Pulvules Trinsicon® (hematinic concentrate with intrinsic factor, Lilly), in bottles of 60 and 500. [032566]

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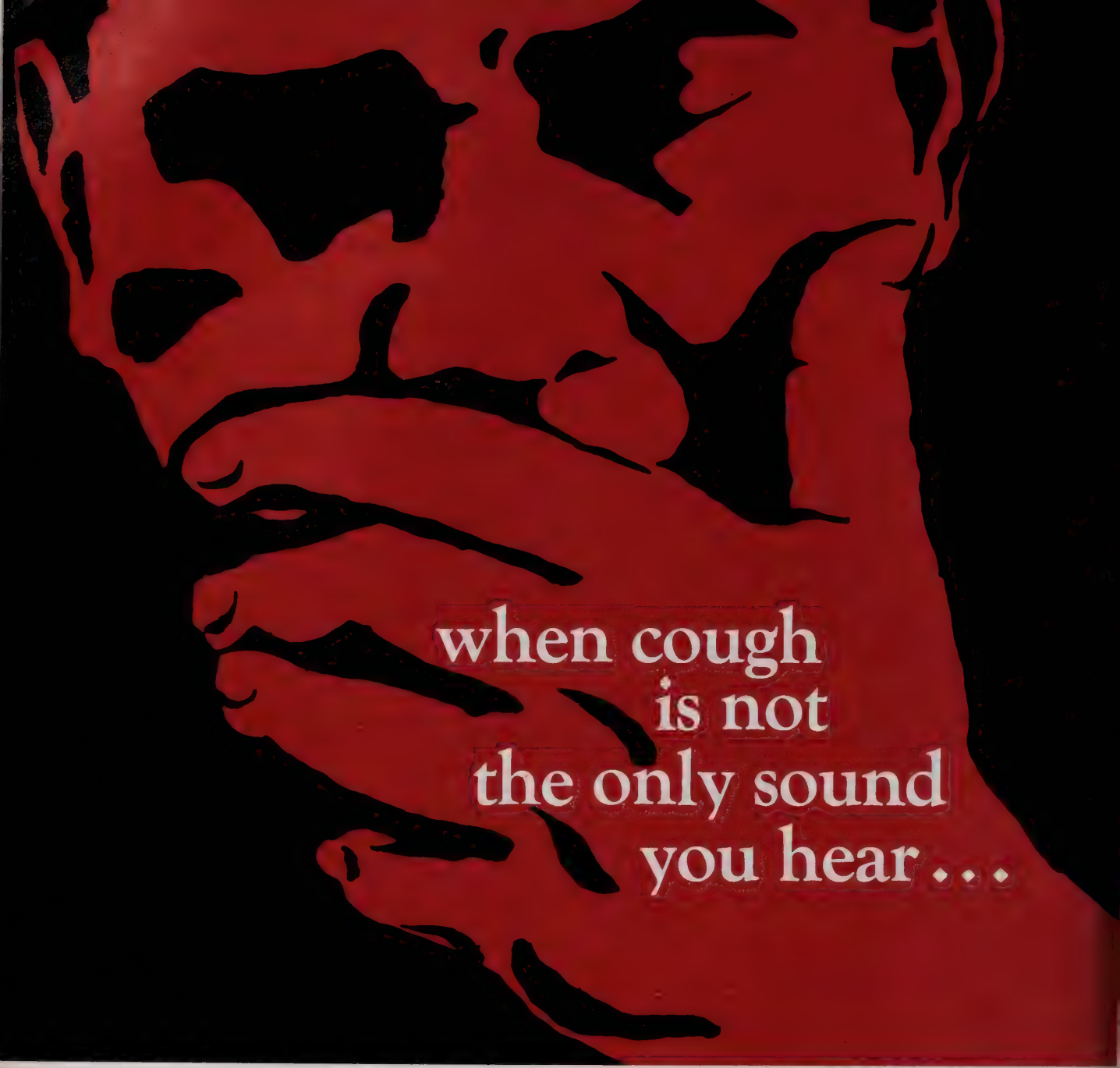
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Available on prescription only. Class X exempt narcotic. Permissible on oral prescription.

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Side Effects: Minimal, but when encountered may include jitteriness, nausea, drying of mouth, insomnia, constipation, which disappear upon adjustment of the dose or discontinuance of treatment.

Precautions and Contraindications: For complete detailed information, refer to package insert or official brochure.

Strasenburgh

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Editorials

The Vineberg

*"Chirurgic is too important a branch of medicine to leave to the Chirurgeons."**

MANY SOURCES of extra-coronary blood supply have been brought to the heart of dog and man by ingenious surgeons during the past 25 years. Interest today, however, centers about the left ventricular implantation of internal mammary arteries, the Vineberg procedure.[1] Variations of this procedure with one internal artery implanted, with two vessels used, one anteriorly and one posteriorly, and with other modifications have been done in over 500 cases at the Cleveland Clinic. They indicate that 90 per cent of the implanted arteries stay open.[2] Operative mortality is reported from 4 to 7 per cent.[3] The late mortality is in the neighborhood of 10 per cent.[4]

In patients with severe angina pectoris the clinical results are stated to be excellent. But there is a large placebo effect to be discounted, especially noted in the good results of simple internal mammary artery ligation, or even of a sham thoracic incision.[5]

Sones et al. demonstrated angiographically that the coronary circulation could be filled from the implanted mammary vessels.[6] A recent study by Gorlin and Taylor suggests that the operation is followed by a slight change from anaerobic to aerobic myocardial metabolism.[7]

The Vineberg procedure and variations thereof will be tried in many centers in the immediate future. These operations, however, must still be considered to be in an experimental stage. Anatomical demonstration of cross-connections and patency are of interest, but what is needed is evidence of blood flow through the new channels. Comparative data on operated and nonoperated groups of patients also must be accumulated, showing changes in recurrence of myocardial infarction and mortality.

Centers electing to proceed with this therapy should consider Sabiston's[8] indications: 1. An established diagnosis of coronary arterial occlusion by arteriography, 2. Uncontrolled angina pectoris, and 3. Evidence that there has not been an acute myocardial infarction in the previous four to six months.

Any group of anginal patients subjected to surgery for relief of pain will be, selectively, those patients who react poorly to pain, and those patients who seek maximal therapy, i.e., surgery for pain. These include the neurotic patients who, though they may be demonstrated to have coronary disease, may actually suffer from the neurosis rather than the arteriosclerosis. Patients chosen for surgery

*Post Talmudic aphorism attributed to Rabbi ben Jácob.

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Use cautiously in patients with severe hypertension, diabetes mellitus, hyperthyroidism or urinary retention.
Caution ambulatory patients that drowsiness may result.

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"Nothing else I've tried seems to work, so I decided to give you a crack at it."

should first be evaluated by a cardiologist. Demonstration of coronary disease, even severe coronary disease, is at present an inadequate indication for surgery in the absence of related symptoms, especially incapacitating angina pectoris.

Myocardial infarction has its highest mortality in the first six months, during which the danger of surgery is greatest. After this period the low mortality from the disease must be considered along with the mortality from surgery. Thus myocardial infarction alone affords unsure grounds for surgical intervention. Whether or not patients in heart failure may be benefited by this type of surgery is at present unknown. Internal mammary implantation should prove its value in severe angina before it is extended to other groups of patients in whom the yardstick of pain relief is not available. Pain is a subjective measure fraught with uncertainty.[9] The psychological effect upon the patient whose symptoms will be keenly resolved under *General Anesthesia* by *Vascular Surgery* in an *Open Chest* procedure can be literally overwhelming.

Evaluation of long-term results, of subjects followed five years or more, should decide the issue.

Angiographic demonstration of disease is still too new a method to be considered as an over-riding indication for surgery. Fifteen per cent of young American males dying of trauma in the Korean war had coronary narrowing up to 50 per cent or greater.[10] This group is in need of treatment, but not surgical treatment.

Finally, the evaluation of results must also be made by the medical cardiologist, comparing the operative series of cases with similar groups conventionally treated.

Reuben Berman, M.D.
Minneapolis, Minnesota

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*Jacob Braude: Speaker's Encyclopedia.

Men's virtues have their seasons even as fruits have.—Unknown

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Side Effects: Skin rash; gastrointestinal disturbances (chiefly nausea), weakness, dizziness. These seldom require cessation of therapy, and can be relieved by reducing dosage or correcting electrolyte imbalance.
Warning: Enteric coated potassium tablets have been implicated in small bowel lesions and should be used only when adequate dietary supplementation is not practical.

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400-8

The Immune Globulins

In the July 1967 issue of MINNESOTA MEDICINE* is a comprehensive review of the knowledge which has been gained within the past 15 years on the subject of immunoglobulins. Today the well equipped clinical laboratory is able to recognize the various types of immunoglobulins, and this ability has become useful not only in the management of immune globulin disorders but of disorders of the protein metabolism in general.

The immune globulins are a distinctive group of proteins. Their electrophoretic mobility at pH 8.6 is slower than that of other serum proteins. They contain light chains within their molecule, which lack methionine as well as carbohydrate components. These qualities, particularly the absence of carbohydrates, appear to account for their peculiar type of solubility which was recognized in 1847 by Henry Bence Jones. This solubility factor has been used in the diagnostic test for light chain proteins small enough to traverse the glomerular filter and appear in the urine. To this day they bear the name of Henry Bence Jones. Carbohydrates, particularly sialic acid, appear to be involved in the mechanism of solubility of proteins[1].

If light chains can be produced in excess, so might heavy chains. This was indeed reported three years ago by Franklin and associates[2]. A protein of the molecular weight of 53,000 appeared in the serum as well as in the urine of Franklin's patients. No additional cases of heavy-chain disease have turned up since that time, in spite of diligent search by investigators here and abroad.

The spectacular findings of deficiency states of immunoglobulins have lent considerable impetus to the search for deficiency states of proteins outside the small group of immunoglobulins. Complete absence of serum albumin was encountered by Bennhold[3] in two otherwise healthy adult siblings. Additional cases have been discovered since. This recessively hereditary defect must worry physiologists considerably since these patients have only minimal or no edema in spite of absence of albumin and the finding of oncotic† pressures which are barely one half of the normal level.

It was only a matter of time before deficiencies or absence of other plasma protein components were discovered. The deficiency of antitrypsin, an α_1-globulin, appears to be associated with obstructive pulmonary disease[4]. Deficiency states of thyroxin binding globulin[5] and cortisol binding globulin[6], both α_1-globulins, have also been recognized. Deficiency of ceruleoplasmin, (an α_2-globulin) in Wilson's disease is well known. Haptoglobin deficiency has been recognized and described repeatedly[7,8].

Transferrin deficiency has been encountered on at least two occasions[9,10]. As might be expected, this abnormality presented itself as a refractory iron deficiency anemia. Afibrinogenemia with resultant blood clotting problems is a well established entity.

Though the list is not complete, one can readily appreciate the stimulus which the investigation of immunoglobulins has given to the study of proteins in general. The accumulating information will necessarily elucidate further important facets of human metabolism in health and disease.

Horace H. Zinneman, M.D.
Minneapolis, Minnesota

*O'Sullivan, Michael: Immunoglobulins. Minnesota Med. 50: 1113, 1967.

†See Test Your Word Score Page 937.

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Surgery for Otosclerosis *

THE SURGICAL treatment of otosclerosis offers prospects of restorative results of a very high order. Throughout the history of surgery, two things have been uppermost in the thinking and philosophy of the surgeon: the elimination of disease and the restoration of useful function. Surgery for otosclerosis is in the second category. The operation makes no attempt to eliminate all of the diseased tissue. The principle of the operation is to provide a detour around the diseased structures so that vibrations can again reach the nerve endings of the inner ear.

Sound reaches the ear as vibration in air. These vibrations enter the external auditory canal where they set the tympanic membrane into motion. This motion is transmitted through the chain of auditory ossicles to the fluid surrounding the sensory hair cells in the inner ear. Because fluid is incompressible the vibration must travel through the inner-ear fluid with a wave motion. This requires two openings in the bony walls of the cochlea. The first exists at the oval window into which the footplate of the stapes fits. The second exists at the round window, where a thin membrane allows the energy of the vibration to escape. Blocking of either window will create the symptoms of a conductive or mechanical hearing loss. Blocking of both windows creates the symptoms of a neural hearing loss.

Otosclerosis most often involves the region of the footplate of the stapes, obliterating the joint between the otic capsule and the stapes and thus interfering with transmission of sound. Restoration of a movable system effectively restores hearing. Less often, otosclerosis involves the bony wall of the otic capsule overlying the cochlea. In this instance, direct damage is done to the nerve with loss of nerve function. This type of hearing loss is not favorably influenced by surgical treatment. Otosclerosis rarely closes the round window to the cochlea; in this circumstance, improvement by surgical treatment has been reported in a few cases, although the prospect of improvement is limited.

At the present time the surgical treatment of otosclerosis may be compared with cataract surgery as a means of improving one of the special senses. The operation may now be done with a high degree of success but not without a small risk of further damage. Fortunately, if the operation is done on the ear with poorer hearing, the patient's handicap is not usually increased by an unsuccessful operation. Operation is not advised when it must be done on the only ear with hearing. Patient response to an operation which restores a wanted function is extremely gratifying. The patient whose hearing is restored after years of impairment is much more profuse in his expression of appreciation than is the patient who has been relieved of annoying symptoms or of risk by an operation on the mastoid.

Kinsey M. Simonton, M.D.
Rochester, Minnesota

*House, H. P.: Surgery for Otosclerosis. Minnesota Med 50:817, 1967.

Polyhydramnios *

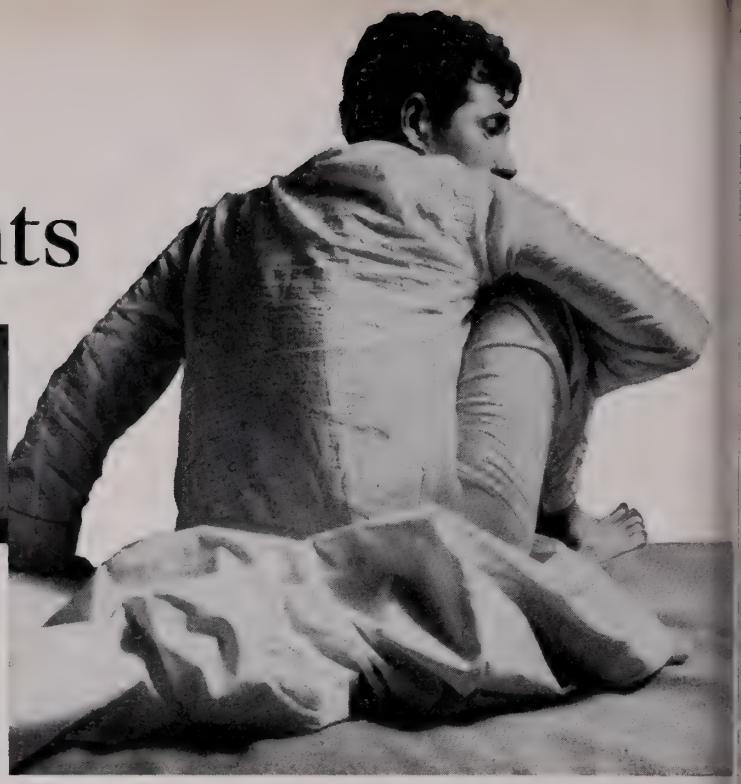
POLYHYDRAMNIOS is a rare but significant complication of pregnancy in which there is an excessive accumulation of amniotic fluid within the uterus. Most obstetricians consider an amniotic fluid volume of more than 2,000 ml. to represent polyhydramnios; the condition is classified as mild, moderate, or severe. Chronic polyhydramnios, which usually becomes detectable over a period of many days or even weeks, occurs once in approximately every 175 deliveries. The acute variety of the disease, which develops in a few days, is even more rare, occurring only once in about 12,000 deliveries.

The cause of polyhydramnios continues to be poorly understood. No abnormalities can be detected in the membrane of the amniotic sac

*Barr, L. W., and Neel, H. B.: Duodenal Atresia and Maternal Hydramnios. Minnesota Med 50:491, 1967.

Open-eyed nights





Too tense to sleep...too tired to get up. **Early to bed, late to rise, and not much sleep at that, the patient with severe psychic tension is understandably tired. His tensions and overreactions to the day's stresses may interfere with proper sleep, and his inability to face the day's activities can produce an ever-worsening pattern. By relieving psychic tension, Valium® (diazepam) facilitates sleep, particularly with an h.s. dose. In many patients, the usefulness of Valium has been demonstrated in relieving psychic tension alone or with secondary depressive symptoms. Valium is generally well tolerated and, with proper maintenance dosage, usually does not unduly impair mental acuity or ability.**

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Contraindications: Known hypersensitivity to drug; children under 6 months of age; acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in treatment of psychotic patients, and should not be employed in lieu of appropriate treatment. As with most CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increase in dosage of standard anticonvulsant medication; abrupt withdrawal in such cases may also be associated with temporary increase in frequency and/or severity of seizures. Advise patients against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance. Keep addiction-prone individuals (such as drug addicts or alcoholics) under careful surveillance because of their predisposition to habituation and dependence. Use of any drug in pregnancy, lactation or in women of childbearing age requires that potential benefit be weighed against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam), such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. Employ usual precautions in the severely depressed or in those with latent depression; suicidal tendencies may be present and protective measures necessary. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation (initially 2 to 2½ mg once or twice daily, increasing gradually as needed or tolerated).

Adverse Reactions: Side effects most commonly reported: drowsiness, fatigue and ataxia. Infrequently encountered: confusion, constipation, depression, diplopia, dysarthria, headache, hypotension, incontinence, jaundice, changes in libido, nausea, changes in salivation, skin rash, slurred speech, tremor, urinary retention, vertigo and blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued. Because of isolated reports of neutropenia and jaundice, periodic blood counts and liver function tests are advisable during long-term therapy. Minor changes in EEG patterns (low-voltage fast activity) observed during and after therapy and are of no known significance.

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useful for the relief of psychic tension, alone or with associated depressive symptoms

or in the contents of the fluid. Indeed, even the intra-amniotic fluid pressure is usually recorded as normal in patients with polyhydramnios. When the fetus has a major central nervous system anomaly, such as anencephalia* or spina bifida, it is speculated that the exposed meninges contribute an excessive amount of cerebrospinal fluid to the amniotic fluid. Fetal central nervous system anomalies are also thought to interfere with fetal swallowing of amniotic fluid and may at times cause excessive fetal urination and congenital gastrointestinal defects of the fetus, such as esophageal or duodenal atresia: factors that contribute to poor resorption of amniotic fluid, and can thus lead to polyhydramnios. Placental vascular system anastomoses between the two fetal circulations are thought to be the principal cause for the increased incidence of polyhydramnios in twin pregnancies. Many consider the chronic fetal anoxia sometimes seen in hydropic infants and infants of diabetic mothers to be the main reason for the increased incidence of polyhydramnios seen in such cases.

If the roentgenogram reveals a fetal congenital anomaly that is incompatible with life (such as anencephalia), induction of labor by amniotomy is indicated. When no major fetal anomaly is found on roentgenologic evaluation, symptomatic treatment and observation are indicated until the fetus reaches viable size (35 to 36 weeks' gestation). If polyhydramnios is severe, hospitalization is best. When respiratory distress is present, elevation of the head of the bed may be required, or the patient may have to sit up in a chair to be comfortable. Diuretics and special diets have been of no help in decreasing the excessive intrauterine accumulation of fluid. As the fetus matures, a repeat roentgenogram may detect an anomaly that was previously missed. In an effort to find the cause of the polyhydramnios, the mother's blood should be checked for irregular antibodies, and the presence of diabetes mellitus should be ruled out.

If the polyhydramnios becomes severe, causing marked maternal respiratory or cardiac embarrassment, before the apparently normal fetus reaches viable size, transabdominal amniotomy is indicated. The placenta should be localized so that it may be avoided and then, with sterile technique, 500 ml. of amniotic fluid may be slowly withdrawn through an 18-gauge spinal needle. This procedure may be repeated daily if necessary. Unfortunately, the withdrawal of the large amount of fluid necessary to give the patient symptomatic relief commonly leads to the onset of labor.

If the pregnancy can be continued until the fetus reaches viable size, labor may then be induced by a transcervical amniotomy with slow release of the amniotic fluid. Because of the dangers of placental abruption and postpartum hemorrhage due to uterine atony, crossmatched blood should be available for transfusion and an intravenous needle should be in place during the amniotomy and labor.

Approximately 25% of the infants delivered from patients with polyhydramnios will have major congenital anomalies incompatible with life. The most common of these anomalies are of the central nervous system, with anencephalia the most frequent. Gastrointestinal system defects, such as esophageal and duodenal atresia, are the next most common but are relatively rare. Circulatory anomalies, hydrops fetalis, and many miscellaneous defects account for the remainder.

Because of other obstetric complications, such as prematurity, prolapse of the umbilical cord, difficulties with infants born of diabetic mothers, and erythroblastosis fetalis, the overall perinatal loss with polyhydramnios is approximately 50%.

A complication of pregnancy, such as polyhydramnios, which is associated with a 50% perinatal loss is certainly significant. For an infant born to a mother with polyhydramnios, the prognosis is guarded until the presence of serious congenital anomalies has been ruled out and until the infant has survived the first days of life.

The basic problem in polyhydramnios is not how to manage the pregnancy associated with excessive amniotic fluid but rather how to prevent the abnormalities that cause such an excessive accumulation of fluid. Unfortunately, no prompt solution to this problem is foreseen.

Leonard A. Aaro, M.D.
Rochester, Minnesota

*See Test Your Word Score Page 937.

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Neurogenic Tumors of the Head and Neck*

ALL TUMORS OF the head and neck region should be removed for diagnosis because of the high incidence of cancer occurring in this region. If the tumor is obviously inoperable, a specimen of tissue should be obtained for diagnosis. This can be done with a Silverman needle, but frequently the pathologist prefers a larger piece of tissue for study. For operable lesions the best practice is total excision of the mass for diagnosis preferably by fresh-frozen section technique. If further surgery is indicated (such as a radical neck dissection) it can be carried out at the time of the biopsy procedure—there is no better time to do it. In almost all instances the patient should be under general anesthesia which would permit proceeding ahead with definitive treatment.

If the surgeon practices in this way it is essential that the best preoperative diagnosis possible be established and discussed with the patient so that he is prepared for the necessary treatment whatever it might be. Although many types of lesion occur in the head and neck, it is often possible to establish the correct diagnosis by careful evaluation of the history, physical findings, and results of laboratory studies. All neck structures and the entire oral cavity and larynx must be carefully examined.

Neurogenic tumors usually have been present for a period of years, showing slow growth. They are occasionally painful or tender. They may be multiple. On physical examination the lesion is most often well encapsulated, fusiform in shape, rather rubbery-firm on palpation, and lying in the direction of a major nerve. Other unassociated lesions are usually absent. The greatest difficulty in diagnosing this lesion preoperatively comes from failure to consider it because of its infrequent occurrence.

Oliver H. Beahrs, M.D.
Rochester, Minnesota

*Krause, L. G., and Tomasisi, Simon: Neurogenic Tumors in the Head and Neck. Minnesota Med 50:637, 1967.

Test Your Word Score

Urachus—*a functionless cord of fibrous tissue extending from the bladder to the umbilicus* (page 900).

Consanguinity—*close blood relationship* (page 902).

Olfaction—*the process of smell* (page 902).

Conjugate—*joined together* (page 902).

Genu valgum—*knock knee* (page 904).

Scintillation—*rapid changes of light intensity* (page 907).

Anisocoria—*unequal size of pupils* (page 912).

Oncotic—*pertaining to, caused by, or marked by, swelling* (page 931).

Anencephalia—*absence of the brain* (page 935).

Phrensie—*obs. for frenzy; derangement of the mind* (page 945).

Sequestrectomy—*surgical removal of a piece of dead bone, separated from the live, sound bone* (page 949).

Education is a companion which no misfortune can depress—no crime destroy—no enemy alienate—no despotism enslave. At home, a friend; abroad, an introduction; in solitude, a solace; and in society, an ornament. Without it, what is man?—a splendid slave, a reasoning savage.—Varle

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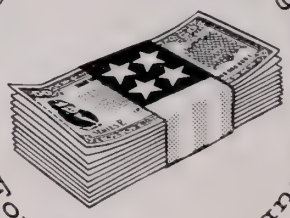
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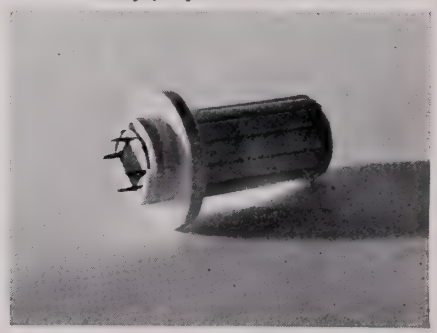
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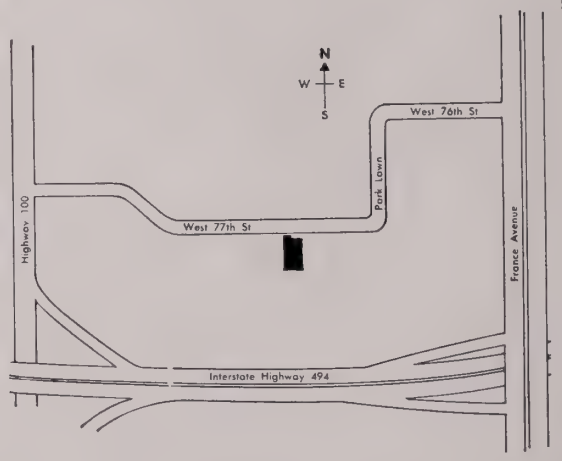
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The Editor's Soliloquy

Physicians in Glass Hospitals

Opposition to the Long Amendment*, by the Minnesota and other Medical Associations, can undoubtedly share credit for its defeat in the first session of the 90th Congress. The Amendment suggested a federal formulary to govern the use of drugs in federal health care programs. Senator Long has publicly stated that the formulary system has attained acceptance in many hospitals of the country and that to extend these same principles to the area of outpatient governmental programs should afford no inconvenience.

The Minnesota Medical Association has generally opposed legislation which would handicap the physician in discharging his responsibility to his patients. In view of the willingness with which many doctors accept the dictates of their own hospital formularies, which encourage drug substitutions, it seems paradoxical that Long's federal restrictions should have met with such vigorous opposition from the medical profession. Why can't they be consistent?

Surely the physician should be allowed complete freedom to discriminate between different brands of the same drug when treating the acutely ill patient. Whether or not the subtle variations claimed by different manufacturers make any difference, it should be the physician's privilege and his responsibility to discriminate. Still it is in many of their own hospitals where some physicians have permitted non-medical persons to decide which drugs are best for their patients by requiring them to abide by the hospital's formulary. This is in effect nothing more than a system of "cracker barrel" prescribing.

That the motives of these administrators and their economic arguments are fallacious is apparent when one considers that the *wrong* drug for any patient could actually increase the total cost of hospitalization by delaying recovery or necessitating the use of another more expensive prescription when the substitute drug was not effective.

The method now used in some hospitals, seeking to control drug use, is to have a "no substitution" block on the prescription blank. If the doctor does not check the space, substitution is assumed to be authorized. This would seem to constitute an act of delegating a medical discretion. Other hospital pharmacies using a more insidious approach to restricting drug usage merely refuse to stock items which they prejudge to be unnecessarily duplicative.

Regardless of the means by which drug substitution is "authorized," the matter of liability has not been clearly decided; but the position of the AMA is that no physician can legally delegate "medical discretion of judgment" to a non-physician, and therefore, cannot properly authorize substitution without specific permission.

If a patient were to suffer death or injury resulting from the use of a substitute drug under a formulary system, the attending physician, the hospital and the pharmacist would share liability. It is possible, also, even with generic prescribing, that the physician can be held liable if the plaintiff is able to show a difference in therapeutic properties of drugs which fall under the same generic name. From the viewpoint of possible legal liability, drugs from trusted manufacturers whose resources may adequately cover lawsuits would seem to be preferable.

If physicians are to be successful in their efforts to preserve freedom from further bureaucratic regulation, their actions at home must be consistent with their arguments to the lawmakers.

Restrictions on drug prescribing must be actively opposed in the hospital as well as in Washington if physicians are to preserve the prerogatives of their profession and provide quality medical care to all Americans.

Carl O. Rice, M.D.

*S-2299, to the Social Security-Medicare Benefits Bill—Reintroduced 2nd Session as S. 3323.

Old Doc Hess says: If your husband becomes impossible, undress him in your mind, put short pants and a Buster Brownie on him and treat him accordingly.

COR

Distinguished Service

Distinguished Service Award



John P. Medelman, M.D.

Dr. John P. Medelman was honored recently in Rochester by his physician colleagues as recipient of the 1968 Minnesota State Medical Association's Distinguished Service Award. The presentation was made at the annual banquet held during the Annual Meeting of the Association.

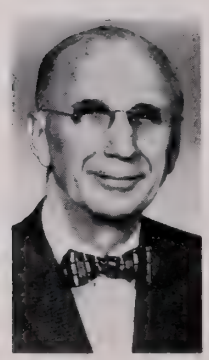
The award is the highest, bestowed by his colleagues, on a Minnesota physician who has made a notable contribution to medical science and the work of the Association. The recipient is selected by a committee of the Minnesota State Medical Association Council.

Dr. Medelman, born on a farm near Devils Lake, North Dakota, received his medical education at Rush Medical College in Chicago. He came to Minnesota, and did post graduate work and trained in Roentgenology. He has served on the staff of St. Joseph's Hospital for over 30 years, ultimately as director of the Hospital's school of X-ray technology and planner of its cobalt section.

Active in the Association, he has served as chairman of various committees and as a council member. He was state president in 1964 and is currently an alternate delegate to the AMA.

Dr. Medelman was a member of the State Board of Medical Examiners and served as its secretary for many years. He is a past president of the American Roentgen Ray Society and a member of the American Board of Radiology.

Citations of Merit

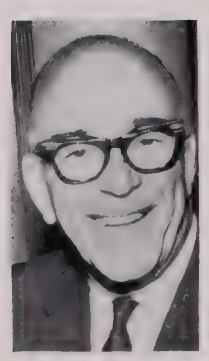


Harold S. Diehl, M.D.

Two special citations of merit were awarded to Dr. Harold S. Diehl and Dr. Ejvind P. Fenger.

Dr. Diehl, medical educator and administrator, was Dean of Medical Sciences at the University of Minnesota from 1935 to 1958. Upon his retirement from the University he became director of research for the American Cancer Society.

Dr. Fenger worked toward Minnesota's tuberculosis control for over 30 years. He was medical director of Glen Lake Sanitorium and is now serving as Director of Tuberculosis Services of Minnesota. Recently Dr. Fenger was named to the American Thoracic Society. This is an honor bestowed on individuals with a high achievement and signal contributions in the field of tuberculosis or other respiratory diseases.

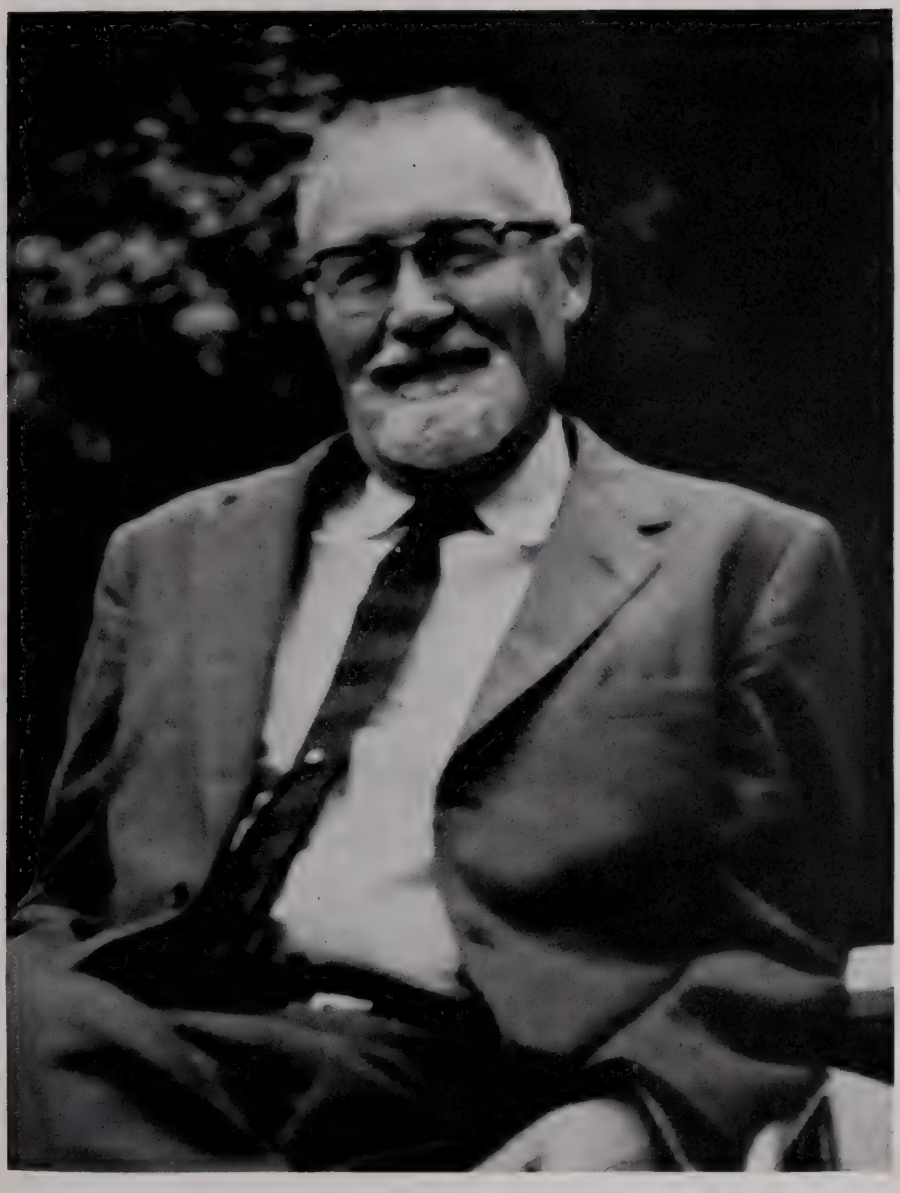


Ejvind P. Fenger, M.D.

Scientific Exhibit Award

A medal for the outstanding scientific exhibit at the Minnesota State Medical Association's annual meeting was presented by the Southern Minnesota Medical Association to Doctors N. K. Jensen, W. R. Schmidt, J. J. Garamella, M. F. Lynch, A. M. Bilgutay and W. D. Kelly of Minneapolis. The exhibit's title was "Cardio-Thoracic Surgery."

Senior Educator



Reynold A. Jensen, M.D.

On July 1, 1968, Dr. Reynold A. Jensen will resign as Medical Director of the Division of Child Psychiatry, Department of Psychiatry and Neurology at the University of Minnesota, a post he has held since 1952. His decision to be relieved of the administrative responsibilities of the Division of Child Psychiatry was not easy, but it will provide him the opportunity to explore the area of communication during a sabbatical leave, a subject which has been of great interest and concern over the years.

Dr. Jensen's association with the University of Minnesota Medical School dates to 1935, when he graduated from that School. During this time, he has participated in the growth of child psychiatry there. This work culminated in 1952 when an inpatient children's unit was established. No one

single person in the state of Minnesota has been so clearly associated with the training of physicians in the specialty of child psychiatry, as well as in the teaching of student child psychiatry.

Teaching is Reynold Jensen's greatest love. He is never happier than when he has had a good seminar, supervisory hour, lecture. Also he enjoys running into a former student, who recalls how much he learned from Dr. Jensen.

He is a native of Sleepy Eye, Minnesota, where he graduated from high school in 1920. In 1925 he received a degree from the River Falls State Normal School, River Falls, Wisconsin; in 1963 that college awarded him its "Distinguished Alumnus Award." His M.D. Degree he received from the University of Minnesota Medical School in 1935. The years between 1925 and 1935 were spent in various jobs. He was YMCA secretary of the Milwaukee YMCA, 1925-1926, and director of religious education for the Congregational Church in Milwaukee, from 1926 to 1929. Before he joined the University of Minnesota faculty, Dr. Jensen served as an associate resident in medicine at the Strong Memorial Hospital in Rochester, New York, as a Rockefeller Fellow in Psychiatry at the Institute of Pennsylvania Hospitals, and as a Commonwealth Fellow in Child Guidance at the Judge Baker Guidance Center in Boston, Massachusetts.

Returning to the University in 1938, he was appointed an instructor in psychiatry and pediatrics. In the ensuing years, his interest and enthusiasm for child psychiatry was combined with an abiding concern in the total life of the University of Minnesota. He has never limited his interests to the Medical School, but has always identified himself with the goals and purposes of the University at large.

An important part of Jens' life has been his wife, Lillian, daughter of a Sleepy Eye, Minnesota, farmer. She attended Sleepy Eye High School before entering the University. They were married in the middle of his internship. Lil specialized in mathematics, economics and psychology at the University of Minnesota, then decided on editing. She is currently active in free lance work and technical writing, particularly for the American Hospital Association.

In recent years, Dr. Jensen has become interested in the problems of aging; since 1963 he has been a member of the Community Health and Welfare Councils Committee on Aging. He is also a member of the Community Health and Welfare Council Board of Directors, the Economic Opportunity Committee, and he has chaired a committee reviewing services to the elderly in public housing.

His special interest has been the retarded child. He has served on numerous state and national level boards and committees on retardation and mental health. He has been on the scientific advisory board of the National Association for Retarded Children. He is also a member of the Minnesota branch of the American Civil Liberties Union. For a number of years he has served as an associate editor in the area of child psychiatry for Minnesota Medicine, the official journal of the State Medical Association.

A man's life and contribution is only poorly reflected in the recitation of his numerous memberships and organizations. Far more important is his personal warmth and enthusiasm for teaching and his unselfish devotion to the cause of children in the advancement of the speciality of child psychiatry.

John C. Duffy, M.D.*
Minneapolis, Minnesota

*Department of Psychiatry and Neurology, Division of Child Psychiatry, University of Minnesota Medical School.

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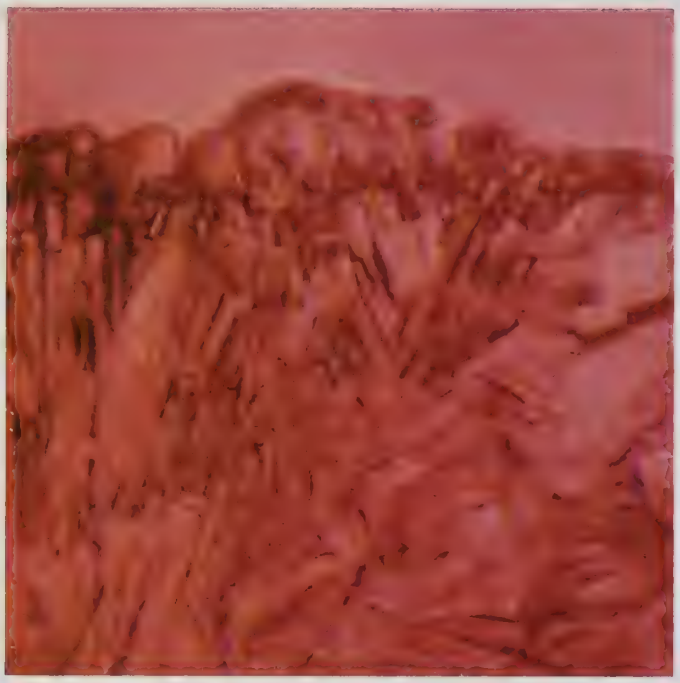
1. Stern, S.B.: Med. Times, Oct. 1967
2. Reports on 1200 patients, data in files, Warren-Teed Pharmaceuticals, Inc. 1966

(See next page for prescribing information)

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microphotograph of magnesium salicylate crystals



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Contraindications: Because of the danger of hypermagnesemia, MAGAN is contraindicated in cases involving advanced chronic renal insufficiency. MAGAN, as other salicylates, may counteract the effect of uricosuric agents, and should not be prescribed for patients on such drugs.

Warning: As with all salicylates, high dosages of MAGAN should be avoided entirely or administered with caution to patients with liver damage, preexisting hypoprothrombinemia, vitamin K deficiency, and before surgery.

Adverse Reactions and Precautions: The same precautions applicable to salicylate therapy in general should be followed in prescribing MAGAN. Appropriate precautions should be taken in prescribing MAGAN for persons known to be sensitive to salicylates. If reaction develops, drug should be discontinued. Dosages of anticoagulants should be reduced with the administration of high dosage levels of MAGAN. *Impaired Renal Function:* Appropriate precautions should be taken in administering MAGAN to patients with any impairment of renal function including discontinuing other drugs containing magnesium and monitoring serum magnesium levels particulariy if dosage levels of MAGAN are high. *Salicylate Poisoning:* Symptoms of salicylism, resulting from high doses of MAGAN, can be expected to resemble closely in character and intensity those associated with aspirin poisoning. These range from dizziness, drowsiness and ringing in the ears to vertigo, convulsions, coma and hypokalemia. Salicylate poisoning can be treated by intravenous fluids with sodium bicarbonate or lactate and potassium supplementation. In very severe cases, hemodialysis may be necessary. Vitamin K, 5-20 mg. orally or slowly i.v., usually restores the prothrombin time to normal.

Dosage: Adults 1 or 2 tablets every 4 hours as required with a full glass of water. In arthritis and other rheumatic conditions, higher doses may be used at the discretion of the physician. The experience with MAGAN in children is limited. The drug should not be used, therefore, for patients below 12 years until indications for use and dosage have been established.

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Breast Cancer

QUESTION: What is the incidence of cancer in the opposite breast with primary operable cancer of the first breast?

ANSWER: The overall incidence of primary cancer in the second breast has been stated to range between 7.5% and 10%, which is about five times greater than in the general population. Urban recently reported on random simultaneous biopsies of the opposite breast in 159 women with primary operable cancers of the first breast. Cancer of the second breast was detected in 19.5% of the cases in that series.

Harold D. Kletschka, M.D.
Houston, Texas

Acute Altitude Sickness

QUESTION: To what pathologic changes are the pulmonary symptoms of acute altitude sickness attributable? Is pulmonary edema a factor?

ANSWER: Individuals rapidly transported to altitudes over 10,000 feet above sea level develop pulmonary symptoms which are well known. This disease entity is referred to variously as acute altitude sickness, high altitude pulmonary edema, mountain sickness, or soroche. It is generally agreed the symptoms are due to hypoxia. These symptoms may occur even in individuals thoroughly acclimatized to living in high altitudes on returning to mountainous areas, for example, after staying at sea level for one to three weeks.

Pulmonary edema may occur in such patients, but the underlying physiopathologic alterations are not clearly established. Acute left ventricular failure or pulmonary venous constriction have been suggested as causative factors.

Treatment in such cases consists of removing the patient to a lower elevation, bed rest, and continuous oxygen administration.

Primrose Tea

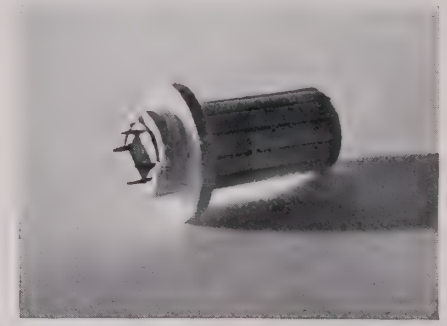
Primrose Tea, drunk in the month of May, is famous for curing the Phrensie. Gerard*

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*See Test Your Word Score Page 937.

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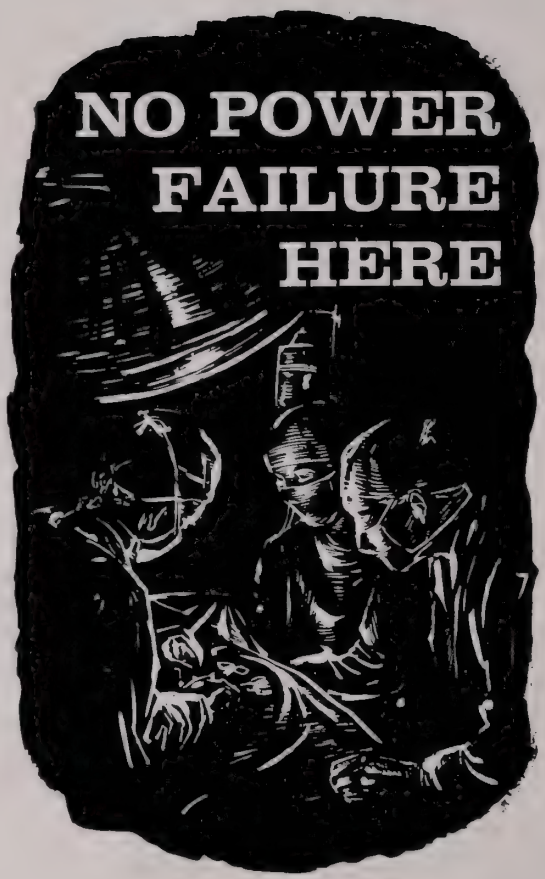
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The Viewing Box

Solitary Lytic Skull Lesion in a Thirteen-Year-Old Male

THIS THIRTEEN-year-old white male was in good health until six weeks prior to admission, at which time he noted the onset of occipital headaches. These occurred occasionally in the morning but were most severe in the evening. There was no nausea or vomiting, and some relief was obtained with salicylates.

Approximately two weeks after the onset of the headaches, the patient noted a tender lump in the occipital area. The bump increased slowly in size during the next four weeks.

Radiographic examination of the skull revealed a destructive punched-out lesion (Arrow, Figure) of the occipital bone. Both the inner and the outer tables of the skull are visible. The border of the lesion is non-sclerotic. A skeletal survey was otherwise negative.

What is your diagnosis? (See next page.)



Figure

Diagnosis. Histiocytosis X (Eosinophilic Granuloma)

The differential diagnosis includes:

1. Cholesteatoma
2. Hemangioma
3. Histiocytosis X (Eosinophilic Granuloma)

Histiocytosis X is a disease entity which includes eosinophilic granuloma, Letterer-Siwe disease, and Hand-Schüler-Christian disease, all of which are phases of a single entity.

Primarily histiocytosis X is a disease of the reticulum cells. Eosinophilic granuloma is the chronic form of the disease and is characterized microscopically by the presence of eosinophilis and histiocytes with areas of necrosis.

Eosinophilic granuloma occurs most commonly between the ages of three and ten. Although rare after fifteen years of age, the disease has been reported in the sixth decade of life. Solitary painful bone lesions are the usual finding, although multiple bones may be involved. Rarely are visceral organs involved.

Biopsy is necessary to make the diagnosis. The prognosis is excellent. Although the lesions tend to heal spontaneously, radiation therapy is the treatment of choice. As little as 50 rads has been reported to eliminate the symptoms within a few hours. The usual dose is 500 to 1000 rads, given in three to four treatments.

John C. Holder, M.D.*
Minneapolis, Minnesota

*Department of Radiology, University of Minnesota Hospitals, Minneapolis, Minnesota.

References

1. Caffey, J.: Pediatric X-ray Diagnosis, 5th Edition, Year Book Medical Publishers, 1967.
2. Edeiken, J., and Hodes, P. J.: Roentgen Diagnosis of Diseases of Bone, Williams and Wilkens Co., 1967

Shakespeare: Diseases
Ague

"He had a fever when he was in Spain;
And when the fit was on him I did mark
How he did shake: 'tis true, this god did shake:
His coward lips did from their colour fly;
And that same eye, whose bend doth awe the world,
Did lose his lustre. I did hear him groan:
Ay, and that tongue of his, that bade the Romans
Mark him, and write his speeches in their books,
Alas, it cried, 'Give me some drink, Titanius,'
As a sick girl."*

*Cassius to Brutus about Caesar in "Julius Caesar" I,2.

The truth is incontrovertible. Panic may resent it; ignorance may deride it; malice may distort it, but there it is.—Winston Churchill, 1915



Fracture Conference

Ununited Fractures of Lower Third of Tibia*

Dr. Mark B. Coventry:†

We are going to talk about ununited fractures of the lower third of the tibia.

Case 1

Dr. Edwin L. Laurnen:‡

The first case is that of a 40-year-old housewife whose history dates back to 1952 when, at age 25, she sustained a fracture of her right tibia and fibula while skiing. Her home physician treated this by open reduction and plate fixation. The fracture was complicated by infection at this time in 1952 and she had numerous sequestrectomies§ and other treatment in order to curb the infection. However, she seemed to get along fairly well, and resumed her skiing until April 1959, when she refractured the tibia and fibula. The fracture was treated by grafting with autogenous iliac bone; but she continued to have pain and disability in the leg. Thus, when she was first seen here in April 1967, she had been having difficulty with this extremity for 15 years. The roentgenographic appearance of the leg is shown in Figure 1-A and B. Clinically, she had posterior bowing of 30° and, not apparent in the roentgenograms, 30° of internal tibial torsion.

Dr. Coventry:

On the lateral roentgenogram note the degenerative change at the posterior one third of the ankle joint. Dr. P. J. Kelly and I have been especially interested in this phenomenon. The marked posterior bowing produces these degenerative changes in the posterior aspect of the talotibial joint. Dr. Enneking is visiting here today, and we are going to start working him hard early this morning by asking him to comment on these patients before we tell you what we have done.

Dr. William F. Enneking:¶

Do you know whether the posterior angulation persists from her first injury or is this a shift?

Dr. Laurnen: I don't know for certain.

---

*Held January 15, 1968.

†Professor of Orthopedic Surgery, Mayo Graduate School of Medicine (University of Minnesota) and Consultant, Section of Orthopedic Surgery, Mayo Clinic, Rochester, Minnesota.

‡Resident in Orthopedic Surgery, Mayo Graduate School of Medicine (University of Minnesota), Rochester, Minnesota.

§See Test Your Word Score Page 937.

¶Professor of Orthopedic Surgery, University of Florida, and visiting orthopedic professor at the Mayo Graduate School of Medicine, January 15 to 17, 1968.

Dr. Enneking: You don't know how much displacement there was on refracture?

Dr. Laurnen: No. The second fracture occurred in April 1959.

Dr. Coventry:
It is important to remember that she has a 30° internal torsion deformity of the distal tibial fragment. She walks very pigeon-toed. That doesn't show on these films.

Dr. Enneking: How long after the second injury was this film made?

Dr. Laurnen: Eight years.

Dr. Coventry: Her complaint now is deformity and pain?

Dr. Laurnen: Yes, and limb shortening.

Dr. Coventry: Is there any drainage now?

Dr. Laurnen: No.

Dr. Enneking: Obviously, from the standpoint of (1) activating her infection and (2) changing the relationship between the talus and fibula, it

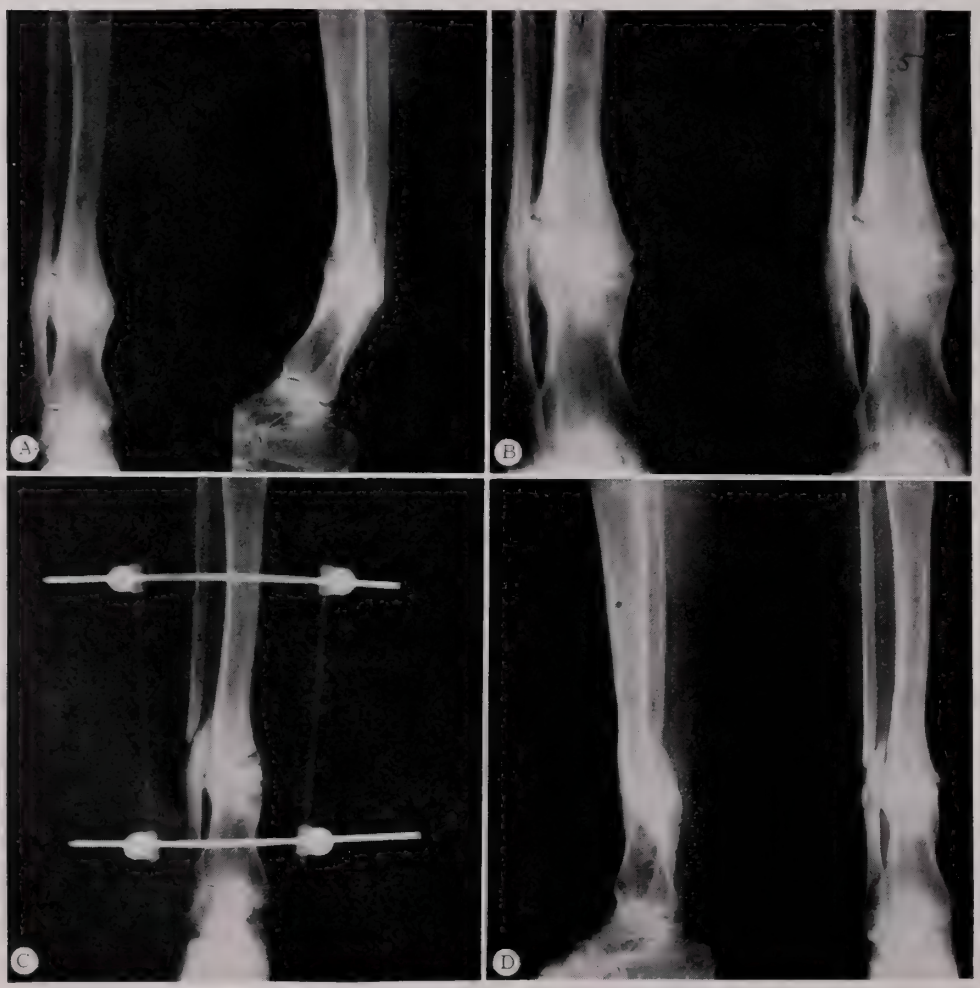


Fig. 1—*A*, Forty-year-old housewife with pain, deformity, and fibrous union of an old fracture. *B*, Anteroposterior tomograms of old fracture with fibrous union. *C*, Appearance after wedge-osteotomy correction of deformity, grafting, and incorporation of Roger Anderson apparatus. *D*, Five months after corrective operation and use of onlay grafts.

would be extremely hazardous to try to correct her deformity. As long as she isn't having drainage and significant pain, and if she would accept her deformity, I suspect I would probably let it go at that. If I had to try to correct it, I would probably try to make the correction a good distance from the old injury if she wasn't having drainage. I thought I saw a sequestrum on the tomogram.

Dr. Coventry: How long has she gone without drainage?

Dr. Laurnen: Several years.

Dr. Enneking: I think I would avoid operation if I could find any reasonable way to do so.

Dr. Coventry: She is a young mother and walks with a cane. She has much deformity.

Dr. Patrick J. Kelly:* Is there union or not?

Dr. Coventry: The fragments are ununited, but she has a rather firm fibrous union. Why don't you show Dr. Enneking what we did?

Dr. Laurnen:

In May 1967, shortly after she came, a wedge osteotomy was performed to correct this deformity (Figure 1-C). The base of the wedge was situated posteriorly and medially and two Steinmann pins were placed in the tibia, one proximally and one distally, and incorporated into the Roger Anderson apparatus with some compression. Use of these pins was continued for three months and then they were removed. The cast also was removed and she was placed in a short leg lacer brace. Five months after treatment she had union (Figure 1-D) and seemed to be having a satisfactory result from surgery. The fibula was osteotomized at the time the deformity was corrected.

Dr. Coventry:

She had no drainage. We used small sliver-like onlay grafts a la Phemister.[1,2] We took these from the valgus part of the pseudoarthrosis, that is, the adjacent bone, and laid them over the osteotomy site. One can't put too much bone in this area, as you know, because there is little soft tissue for coverage. There was quite a bit of scarring of the skin in addition. The posterior part of the tibiotalar joint should be noted. It seems to have opened up a bit and I think maybe it will last her a good while. She is walking without a cane and without torsional deformity. A letter received this week indicates that she now has full activity, no deformity, no pain, and a happy result.

Dr. Joseph M. Janes:† What is the cause of the calcification in the Achilles tendon?

Dr. Coventry:

I don't know whether that has resulted from partial rupture of the tendon or from direct trauma. Bony trabeculae are seen on close inspection, so I suppose it is heterotopic bone. Well, let's go to the next patient.

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Case 2

Dr. Laurnen:

Our next patient is a 40-year-old man who also sustained a fracture of his right tibia and fibula while skiing in February 1966. This was treated in his home community by open reduction and insertion of two Rush pins two weeks after injury. Four months after injury the pins were removed and a cast was reapplied for an additional two and a half months. Then he resumed unrestricted weight-bearing six and a half months after fracture. However, he continued to have disability with this extremity and came here 15 months after injury. The roentgenographic appearance of the fracture at that time is shown in Figure 2-A and B.

Dr. Coventry:

Does anyone think this would be a good case, if seen initially, for intramedullary nail fixation? I don't see any show of hands. I would agree. The fracture is much too low and this may have contributed to the nonunion,

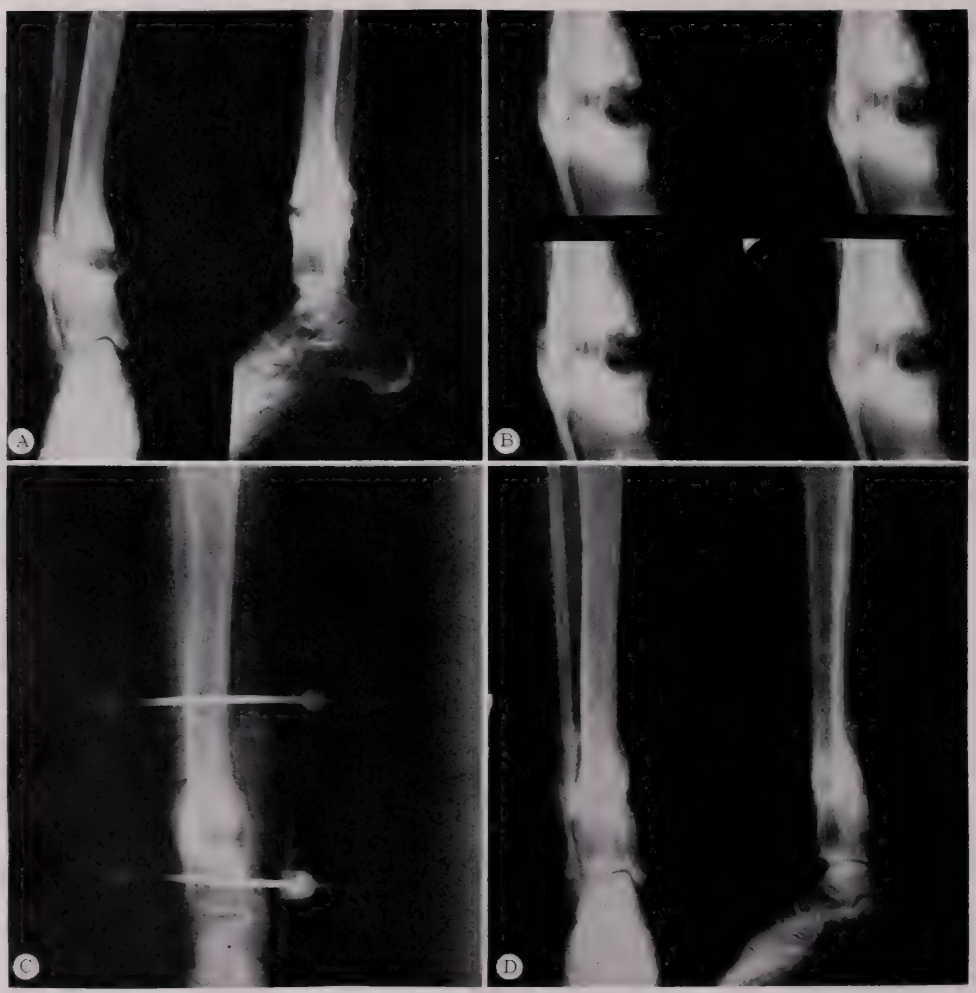


Fig. 2—*A*, Nonunion 15 months after injury. *B*, Anteroposterior tomograms showing nonunion prior to treatment at Mayo Clinic. *C*, Appearance after osteotomy and iliac onlay grafting, showing compression and fixation with Roger Anderson apparatus. *D*, Eight months after treatment of nonunion of tibia.

although we don't know for sure. Dr. Enneking has just come back from two days of skiing, so I thought we would introduce him to the problems of orthopedic practice in the northern part of the country, as opposed to Florida! I suppose you do get water-skiing injuries down there?

Dr. Enneking: They don't break their tibias, though.

Dr. Coventry: Just their necks?

Dr. Enneking: They do that, but they also get anterior dislocations of the hip.

Dr. Coventry: Are there any comments on this fracture?

Dr. Kelly: Is his foot fixed in that amount of equinus deformity?

Dr. Coventry: No, he has a good movable ankle and a normal-looking foot.

Dr. Kelly: And as far as we know, it is not infected?

Dr. Coventry: It is not infected.



Fig. 3—*A* and *B*, Fifty-three-year-old truck driver 1 year after primary open reduction complicated by infection. *C* and *D*, Appearance after correction of deformity and application of Roger Anderson apparatus. *E*, Apparatus as it appeared clinically. *F*, Fourteen months after treatment of nonunion.

Dr. Enneking:

I think I probably would have done an osteotomy of the fibula to align the fracture and would have applied an onlay graft, probably without any internal fixation.

Dr. Laurnen:

Again two pins connected with a Roger Anderson apparatus were used, with an autogenous onlay iliac graft (Figure 2-C). Two months later the Steinmann pins were removed and he was placed in a cast for an additional two months. After four months of treatment the cast was removed. He was placed in a short leg lacer brace with full weight-bearing for two months. The healed tibia is shown in Figure 2-D.

Dr. Coventry:

Again one can see small onlay bone grafts on the roentgenogram. One doesn't have room for much grafting here, and the grafts are put on in barrel-stave fashion. This man is sales manager of a ski company, so it is important to get him back to skiing! He will be going back, I think, later this year.

Two of the residents asked about the external bars of the Roger Anderson apparatus. As you know, Haynes, Stader, and Anderson developed, before World War II, a method of holding fractures externally, without plaster. As a matter of historical interest we will present some data on a patient who was operated on in 1954 for osteomyelitis and nonunion following compound fracture of the tibia and fibula.

Case 3

Dr. Laurnen:

This man was 53 years old when injured. He was a truck driver who, in November 1955, was in a truck accident and sustained multiple injuries involving primarily the lower extremity and also including a fracture-dislocation of the pelvis and hip. He was treated first in his home community and came to the Mayo Clinic for treatment one year after the accident, with the roentgenograms illustrated in Figure 3-A and B.

Dr. Coventry:

He had a complete sciatic palsy on the left and partial sciatic palsy on the right. His urinary tract was functioning fairly well. We thought he would walk again, so we made every effort to correct the infection and nonunion of the tibia.

Dr. Laurnen:

The fractured tibia and fibula originally had been opened and subsequently had become infected. Before he came here several attempts had been made to eradicate the infection. We applied the Roger Anderson apparatus illustrated in Figure 3-C and D. We did one additional sequestrectomy and three weeks later applied only autogenous iliac grafts. Figure 3-E illustrates the apparatus as it appears clinically.

Dr. Coventry:

This treatment was given before the advent of suction-drainage treatment or tubal instillation of antibiotics. Dimethoxyphenyl penicillin (Staphcillin) was not available either. But somehow or other, healing eventually occurred, mostly because of thorough debridement and firm fixation.

Dr. Laurnen:

The Roger Anderson apparatus was left on for three months. A roentgenogram (Figure 3-F) taken 14 months after treatment by this method revealed solid union without evidence of infection.

Dr. Coventry:

The patient returned two months ago with a minor flare-up of infection. We did a sequestrectomy and put in tubes for irrigation-suction and left them in three weeks. This was combined with antibiotic therapy for his *Staphylococcus aureus* infection.

This method of external fixation is occasionally still indicated, and we must all be aware that it is available and helpful in extreme circumstances.

Dr. Kelly:

Was it King[3] that used this same treatment almost routinely for fracture of the tibia? He presented a paper at the meeting of the American Academy of Orthopaedic Surgeons. He sharpened off the end of the tibia, impaled it into the end of the distal part, and then, I think, he used rubber bands to hold the pins together. It sounds Rube Goldberg-like, but it worked fairly well for him. It would be appropriate for a fractured tibia that one wished to treat without the use of metal and that one wanted to stabilize.

Dr. Coventry:

None of these three patients had a fracture that was suitable for compression with internal fixation. There was a bulbous change at the fracture site and we simply could not apply plates because of this bulk. So we used the pins to create and maintain compression. Alignment was maintained with plaster, and the strength of the entire fixation was enhanced by incorporation of the pins and compressing rods in plaster.

Dr. Ronald L. Linscheid:*

The Roger Anderson apparatus is helpful in another circumstance, namely when a fracture of the tibia is accompanied by skin loss, and a skin graft is necessary.

Dr. Coventry:

It is very helpful there. Otherwise, one is working through a hole in a cast, which is not always satisfactory.

Dr. Enneking: How rigid is that fixation?

Dr. Coventry:

It is amazingly rigid, if you follow the basic principles of using enough pins and then getting an oblique cross bar which controls torsion. You simply can't move it—you can pick it up and shake it and it remains rigid.

Dr. Kelly: It was a veterinary apparatus to begin with, wasn't it?

Dr. Coventry:

Well, Stader was a veterinarian, but Haynes, who developed it, was not. I don't know who gets priority.

Dr. Enneking:

We decided to try making a movie to represent a human fracture by taking a roentgenogram of a dog's fracture every hour and then exposing these roentgenograms a few frames at a time so that we could obtain an effect somewhat like that of riffling through an old comic book. A fellow in Ar-

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kansas had made one and it was effective. So one of our fellows flew to Washington and got a dog and put all the "stuff" on it. Even though the dog was restrained and his body was as immobile as we could make it with drugs, every time we exposed an x-ray film the structures had changed just a little so that when we made the movie the appearance was that of a bunch of spaghetti moving around. Our purpose in doing this was to determine whether or not this type of fixation gave absolute immobilization of a fracture and also to determine whether motion, if it did occur, impeded union. Our attempts to do these things failed, but the fracture in the dog did heal nevertheless.

Dr. Coventry:

We have a fair amount of stability by the time we cut these bone ends off and have cortical bone in contact with cortical bone. This gives an inherent, built-in stability, and I think that point is important in the three fractures we have just shown.

Conclusion

These three cases represent the problems associated with long-standing nonunion and sometimes infection of fractures of the tibia. As you can see, alignment, or rather malalignment, is a factor in subsequent degenerative changes in the adjacent joints and surely causes symptoms and produces cosmetic change. Inherent stability of the bones at the site of the corrective osteotomy, adequate fixation externally with pins, and control of infection are necessary to obtain a satisfactory result.

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Edwin L. Laurnen, M.D.†
Einer W. Johnson, Jr., M.D.‡
Rochester, Minnesota

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‡Assistant Professor of Surgery, Mayo Graduate School of Medicine (University of Minnesota), and Consultant, Section of Orthopedic Surgery, Mayo Clinic, Rochester, Minnesota.

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The Diploma Phantom

The diploma gives society a phantom guarantee and its holders phantom rights. The holder of a diploma passes officially for possessing knowledge . . . comes to believe that society owes him something. Never has a convention been created which is more unfortunate for every one—the state, the individual (and, in particular, culture).—Paul Valery

Dermatology

Sunlight Sensitivity

ECZEMA SOLARE (polymorphic light eruption) may develop at any age and usually lasts for many years. Physicians' interest in this disease is greater than before because the disorder is being recognized more readily than previously; however, with the use of new systemic medications, some of which are potential photosensitizers, the increased incidence of this disorder may be partially due to these drugs.

The severity of this disease may be due to many factors, such as duration of exposure, time of year, temperature, etc.; however, the amount of ultraviolet light exposure is the most important variable. The atmosphere scatters the shorter blue light (including the ultraviolet) which gives the sky its blue color. Over three fourths of the ultraviolet light reaching the skin comes from the blue sky and not directly from the sun.

In the spring the patient with cutaneous light sensitivity will be subjected to sufficient quanta of ultraviolet light to precipitate symptoms. The maximum amount of exposure is during June; thereafter the amount decreases, and most patients have little trouble with their disease after early fall, as the sun is close to the southern horizon and the sunlight must pass through a far greater mass of atmosphere than in summer. As a rule, the patients are free of their disease in the winter.



Figure

Generally, within minutes to several hours after the first major exposure to sunlight in the spring, patients experience tingling, burning, and itching on the exposed areas. In most patients the eruption may appear within three to six hours or as much as several days later and can vary from mild erythema to bullous lesions. Because of the protective effect of clothing, the borders of the dermatitis are usually sharp. The differential diagnosis includes lupus erythematosus, erythema multiforme, urticaria, porphyria, ragweed dermatitis, etc. If the condition is unrecognized, chronic erythema and lichenification result and may resemble other eczematous conditions such as atopic eczema, contact dermatitis, or seborrheic dermatitis. The eruption may even extend to those areas not usually exposed to sunlight.

In the treatment of the mild acute eruption, oral antihistamines and topical steroids are used; but if the eruption is extensive, a short course of systemic steroids may be warranted. However, long-term use of oral steroids for treatment or protection is to be avoided. While the eruption is present, further light exposure must be restricted; as the eruption subsides, additional protective measures are instituted.

The only dependable protection is for the patient to avoid that quantity of light exposure which precipitates symptoms. Many patients can tolerate some minutes to several hours of light exposure before eight to nine A.M. and after three to four P.M. To avoid the use of uncomfortable (protective) clothing in summer, one may use topical sunscreen lotions and creams; but the degree of protection is unpredictable, as none of these preparations is ideal. If they stick to the skin, they are usually greasy and prevent sweating; if water-soluble, sweating or bathing removes the protective layer of the sunscreen. In each patient the protective value of any sunscreen can be determined only by usage.

Ramon M. Fusaro, M.D., Ph.D.*
Minneapolis, Minnesota

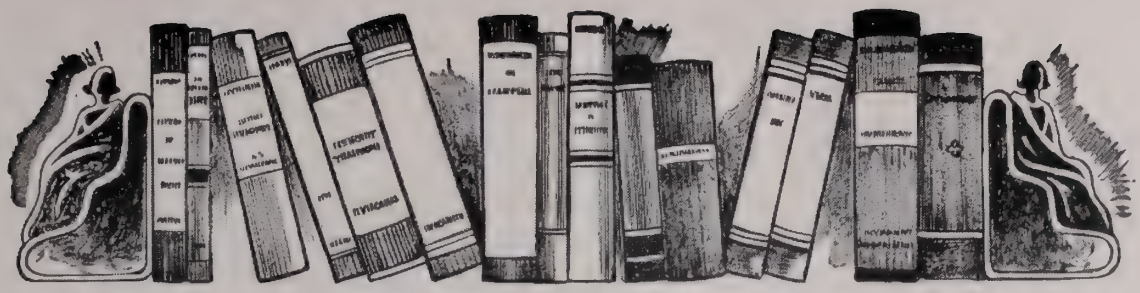
*Associate Professor and Director OPD Dermatology Clinics, University of Minnesota Hospitals.

Automation and Medicine

Since the practice of medicine is essentially the computation of statistical probabilities I think there is little doubt that if all relevant information were stored in one place and made available for computation the accuracy and hence the quality of medical care would be greatly improved . . . The seasoned clinician enlarges his knowledge and improves his statistical calculations as he grows older . . . but most of his acquired information dies with him. The computer remains immortal . . .

This development will not encroach upon the time-honored duties and values of the physician . . . but he will be forced to think quantitatively about the information he obtains. This in itself will greatly increase the value of clinical data and will heighten the perceptions and analytical ability of the physician . . . his personality will remain a deciding factor in the therapeutic process, but he will no longer be forced to call upon his own memory for the complex assessment of the statistical probabilities of each diagnosis . . . Fortified with the vast knowledge of a computer he will more fully develop his own potential as a physician and as a human being.*

*M. Henry Williams, Jr., in Richard M. Magraw: Ferment in Medicine, 1966.



Book Reviews

The Love of Books, the Golden Key That Opens the Enchanted Door.—Andrew Lang

TREATMENT OF HEART DISEASE IN THE ADULT. By Rubin, I. L., Gross, H., Arbeit, S. R., and Hutcheon, D. E. Lea and Febiger, 1968. Philadelphia. 393 pages. Price unknown.

This work is the collaboration of three clinicians at the well known Montefiore hospital in the Bronx (the first three authors) and Hutcheon, in the department of pharmacology of the New Jersey College of Medicine. It is a valuable, authoritative handbook of treatment that will serve as a useful standard of what is being done in adult cardiac therapy in 1968. Particularly helpful are the precise tables and outlines of treatment for such common conditions as myocardial infarction and arrhythmias. No doubt many will object to specific features in an outline of therapy, but it is comforting to know that contained herein are the orders for a myocardial infarction from the pain to the pan to the perambulation.

This is a large book. It measures 9 by 11 inches: very close in size to the Merriam Webster unabridged dictionary—with which an invidious comparison may be made. "Treatment", exclusive of covers, is ¾ inch thick and contains 393 pages. A similar depth of dictionary contains 500 pages; but the serious criticism is that Webster can print over 100 three-column lines to each page compared to about 50 single column lines in the "Treatment" book. The conclusion is inescapable that "Treatment" is turgid. One could condone, even praise the thick glossy paper so inviting to the solution of difficult printing tasks such as x-ray reproduction. Some of the x-rays are indeed fine examples of the art of printing; but most are no better than one would expect on less weighty paper. The words are recommended. The paper, the size, the weight, and the illustrations are not.

The book would be more acceptable as a ¾-inch octavo for an intern's pocket.

Reuben Berman, M.D.
Minneapolis, Minnesota

ULTRASTRUCTURE OF NORMAL AND ABNORMAL SKIN. by Alvin S. Zelickson, 431 pp, 377 illus, $22.50, Philadelphia: Lea & Febiger, 1967.

This book presents a concise and well written survey of the field of electron microscopy. Its emphasis concerns the skin; however, the book should appeal to anyone who is interested in ultrastructure. The advances made and the knowledge accumulated in this aspect of histology have been rapid. It, therefore, becomes a necessity to have an authoritative reference source. This book fulfills that need.

Dr. Zelickson has enlisted highly competent coauthors, each an authority in his respective subject. The result is a well written and remarkably easy to read book on this technical subject. Basic principles concerning the instrument as well as the interpretation of cell ultrastructure are dealt with in the first part of the book. In the latter sections comprehensive coverage is given to more advanced aspects of cutaneous ultrastructure (abnormal as well as normal). As a result this book provides a ready access to much knowledge in this rapidly advancing field.

Willard C. Peterson, Jr., M.D.
Minneapolis, Minnesota

CARDIAC RADIOLOGY. Edward D. Dunne, 246 pages, Lea & Febiger, Philadelphia, 1967.

This book is based on the author's personal experience as a radiologic member of the cardiac team at St. Vincent's Hospital, Los Angeles. The topics discussed are limited to the valvular lesions and the common congenital anomalies, i.e., the sextal defects, patent ductus arteriosus, coarctation of aorta, pulmonary stenosis, and tetralogy of Fallot, with brief excursions into relevant associated lesions.

The sole emphasis of the book is on the findings presented by the routine plain films (the four cardiac views plus an overpenetrated anteroposterior view) and fluoroscopy. These are discussed in great detail and correlated with the results of catheterization, angiocardiography and surgery. The author stresses the importance of fluoroscopic examination, which he feels offers the greatest hope for improved radiologic diagnosis.

The illustrations are of very good quality. The bibliography is relatively small.

This work should be helpful to radiologists, cardiologists and their residents in search for a comprehensive and competent review of the basic roentgen diagnosis of the common cardiac diseases. Some may even be challenged to prove or disprove the value of cardiac fluoroscopy.

S. H. Tsai, M.D.
Minneapolis, Minnesota

In Appreciation

The Minnesota State Medical Association recognizes the valuable contribution made by our technical exhibitors to the success of our recent 115th Annual Meeting. We also recognize that their participation in future meetings is essential if we are to maintain our tradition of outstanding medical meetings. The firms listed below, through their participation in our 1968 meeting, have demonstrated their interest in the Minnesota State Medical Association and our Annual Meetings. We request that our members join us in expressing our sincere appreciation to these firms and their representatives. We believe that each and every member present at our Annual Meetings would find it beneficial to visit the uniformly informative exhibits that these firms provide.

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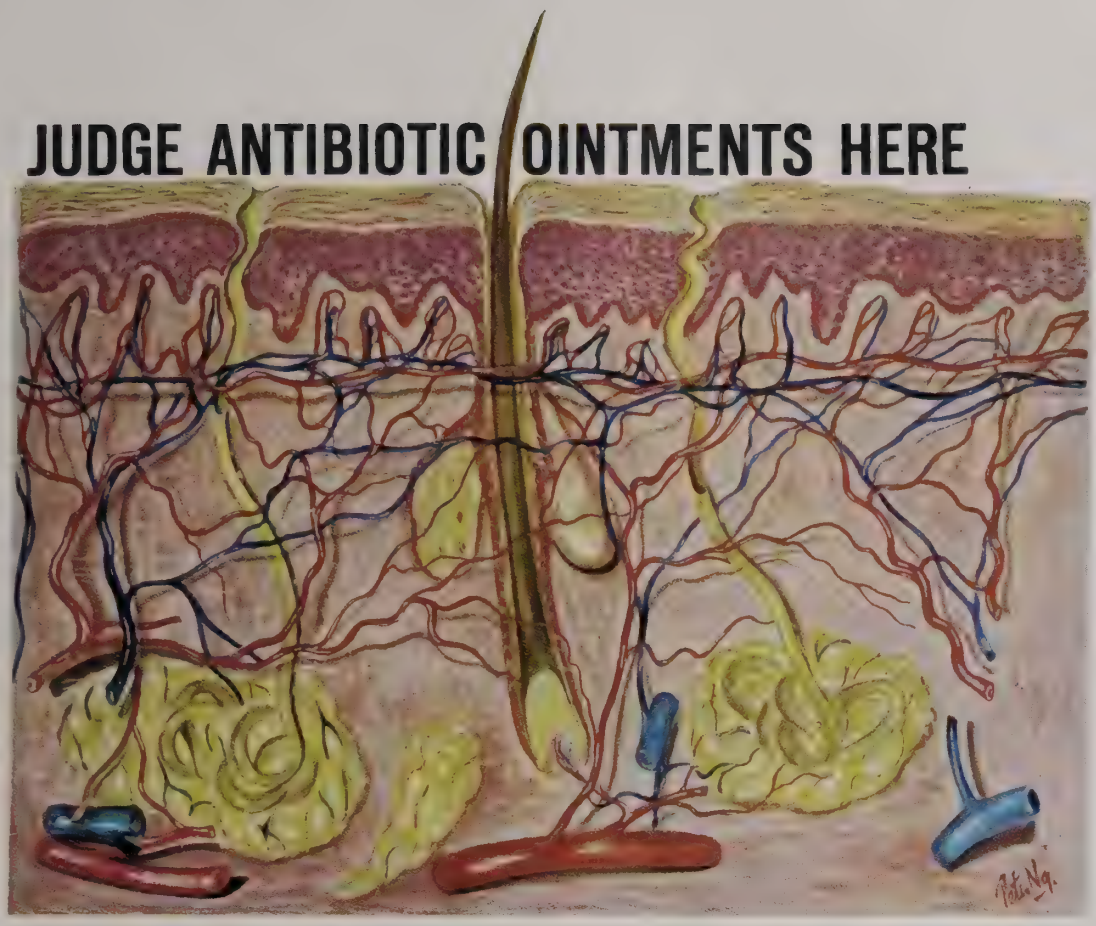
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Complete blood and platelet counts should be done prior to and at regular intervals during treatment with the drug (see recommendations under "Important Note and Precautions") to help in the early detection of serious bone marrow injury. Abnormalities in initial blood tests should rule out use of the drug. Also, patients should be made aware of such early toxic signs of a potential hematologic problem as fever, sore throat, mouth ulcers, easy bruising and petechial or purpuric hemorrhage. Should such signs appear, the patient should be advised to discontinue the drug and to report to the physician immediately.

Indication Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia. It is not a simple analgesic and should never be administered for relief of trivial facial aches or pains.
Contraindication Do not use in those with a known sensitivity to any tricyclic compound or in those being treated with M.A.O.I. agents. As long a period as possible should elapse before using Tegretol in patients who have been treated with M.A.O.I.'s, with a minimum of 7 days. In such cases, initial dosage should be low and the patient's reaction to gradual increments closely observed.
Important Note and Precautions Familiarity with the clinical symptoms which lead to an accurate diagnosis of true trigeminal neuralgia and with the complete prescribing information, careful patient selection, a thorough examination before treatment and close patient supervision throughout the treatment period are essential to the safe and effective use of this drug.
Where feasible, Tegretol should not be used in conjunction with any potent drug which may increase the possibility of toxic reactions.
In pregnancy, the drug should not be prescribed during the first trimester and thereafter only to patients in whom the clinical situation warrants the potential risk. It should not be administered to nursing mothers.
Patients with increased intraocular pressure should be closely observed during treatment with this drug because of its anticholinergic effect.
Because of the drug's relationship to other tricyclic compounds, the possibility of activation of latent psychosis and, in the elderly, of confusion or agitation, should be considered.
Dizziness and drowsiness may occur and patients should be cautioned about the hazards of operating machinery or automobiles and of engaging in other hazardous tasks.
Use cautiously in patients with a history of coronary artery disease, organic heart disease, congestive failure or liver disease.
Before initiating therapy, the following laboratory procedures should be performed:
1. Complete blood and platelet counts which, if abnormal, should rule out the use of the drug.
2. Baseline evaluations of liver function.
During treatment with Tegretol, the following laboratory procedures should be performed:
1. Complete blood and platelet counts should be done at intervals of one week during the first month of drug treatment, every two weeks during the second and third months, and at monthly intervals thereafter for as long as the patient is taking the drug. A trend toward a decreasing white blood cell count should suggest a dosage reduction and more frequent laboratory and clinical evaluations. Should this trend continue, the drug should be discontinued.
2. Liver function tests must be performed at regular intervals during treatment with this drug since liver damage may occur during therapy. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.
3. Periodic eye examinations, including slit-lamp, funduscopy and tonometry, are recommended for patients being treated with this drug since many phenothiazines and related drugs have been shown to cause eye changes.
4. Complete urinalysis and BUN should be done on patients treated with Tegretol because of observed renal dysfunction.
Adverse Reactions Dizziness, drowsiness, unsteadiness on the feet, nausea, vomiting, aplastic anemia, transitory leukopenia, agranulocytosis, eosinophilia, leukocytosis, thrombocytopenia, purpura, abnormalities in liver function tests, cholestatic and hepatocellular jaundice, urinary frequency, acute urinary retention, oliguria with elevated blood pressure, albuminuria, glycosuria, elevated BUN, microscopic deposits in the urine, impotence, disturbances of coordination, confusion, headache, fatigue, blurred vision, transient diplopia and oculomotor disturbances, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, nystagmus, tinnitus, paralysis and other symptoms of cerebral arterial insufficiency, pruritic and erythematous rashes, urticaria, Stevens-Johnson syndrome, photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, alopecia, diaphoresis, recurrence of thrombophlebitis, erythema multiforme and nodosum, aggravation of disseminated lupus erythematosus, gastric distress, abdominal pain, diarrhea, constipation, anorexia, dryness of the mouth and pharynx, glossitis, stomatitis, fever, chills, adenopathy, lymphadenopathy, aching joints and muscles, leg cramps, conjunctivitis, left ventricular failure, aggravation of hypertension, hypotension, syncope and collapse, edema, aggravation of coronary artery disease and congestive heart failure. (Whether these cardiovascular effects are drug-related is not known. However, some of these complications have resulted in fatalities.) The necessity for discontinuing the drug should be dictated by the gravity and severity of the adverse reactions.
Dosage and Administration The drug should always be taken with meals, if possible.
Initial: One-half tablet (100 mg.) b.i.d. on the first day. Thereafter, the dose should be increased in one-half tablet (100 mg.) increments every 12 hours until freedom from pain is achieved. To relieve pain, between 200 mg. and 1200 mg. per 24 hours may be necessary.
Maintenance: Initial control of pain can be maintained in most patients with a dose of 400 mg. to 800 mg. daily. Maintenance doses may range between 200 mg. and 1200 mg. daily.
At least once every 3 months during treatment period attempts should be made to discontinue the drug or to reduce the dose to the minimum effective level.
Availability Round, white, single-scored tablets of 200 mg. in bottles of 100 and 1000. (B)46-820-A
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Indications: Hypertension and many types of edema involving retention of salt and water.

Contraindications: Hypersensitivity and most cases of severe renal or hepatic disease.

Warning: With the administration of enteric-coated potassium supplements, which should be used only when adequate dietary supplementation is not practical, the possibility of small bowel lesions (obstruction, hemorrhage, and perforation) should be kept in mind. Surgery for these lesions has frequently been required and deaths have occurred. Discontinue enteric-coated potassium supplements immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur.

Use with caution in pregnant patients. Since the drug may cross the placental barrier, adverse reactions which may occur in the adult (thrombocytopenia, hyperbilirubinemia, altered carbohydrate metabolism, etc.) are potential problems in the newborn.

Precautions: Antihypertensive therapy with this drug should always be initiated cautiously in postsympathectomy patients and in patients receiving ganglionic blocking agents or other potent antihypertensive drugs, or curare. Reduce dosage of concomitant antihypertensive agents by at least one-half. Barbiturates, narcotics or alcohol may potentiate hypotension. Because of the possibility of progression of renal damage, periodic determination of the BUN is indicated. Discontinue if the BUN rises or liver dysfunction is aggravated. Hepatic coma may be precipitated.

Electrolyte imbalance, sodium and/or potassium depletion may occur. If potassium depletion should occur during therapy, the drug should be discontinued and potassium supplements given, provided the patient does not have marked oliguria.

Take special care in cirrhosis or severe ischemic heart disease and in patients receiving corticosteroids, ACTH, or digitalis. Salt restriction is not recommended.

Adverse Reactions: Nausea, gastric irritation, vomiting, anorexia, constipation and cramping, dizziness, weakness, restlessness, hyperglycemia, hyperuricemia, headache, muscle cramps, orthostatic hypotension, aplastic anemia, leukopenia, thrombocytopenia, agranulocytosis, impotence, dysuria, transient myopia, skin rashes, urticaria, purpura, necrotizing angiitis, acute gout, and pancreatitis when epigastric pain or unexplained G.I. symptoms develop after prolonged administration. Other reactions reported with this class of compounds include: jaundice, xanthopsia, paresthesia, and photosensitization.

Average Dosage: 50 or 100 mg. with breakfast daily or 100 mg. every other day.

Availability: White, single-scored tablets of 100 mg. and aqua tablets of 50 mg., in bottles of 100 and 1000.

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For full details, please see the complete prescribing information.

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Clinical Path Conference

Fulminant Meningococcemia

Case Report

THIS 22-YEAR-OLD white male draftsman was hospitalized for the acute onset of headache, vomiting, chills and muscle pain.

Past History

Thirteen years prior to this admission the patient had suffered an attack of poliomyelitis with transient paraparesis from which he had completely recovered. One year prior to this admission he had had an illness characterized by the rapid development of severe headache, vomiting, generalized muscle aching and fever. He was seen in the emergency room of Hennepin County General Hospital and was observed to have a temperature of 102 degrees and a questionably stiff neck. A lumbar puncture was performed and the cerebrospinal fluid was found to be normal and sterile on culture. His white blood count was 14,400 with 91 per cent neutrophils. Urinalysis was normal. He was discharged from the emergency room but was subsequently hospitalized elsewhere and treated for five days with penicillin. According to the patient, he was told that he had had "a bad case of flu." He made a full recovery.

Present History

Ten hours after the onset of his first symptoms he was admitted to the hospital, complaining of a severe frontal headache, some stiffness in his neck and leg muscles, chills and vomiting. Although he was a husky young man, he appeared acutely ill but was fully oriented. Temperature was 103 degrees; blood pressure 112/60; pulse 120.

Physical Findings

The eyes, including the optic fundi, were normal. Mild pharyngeal injection was observed but there was no exudate present. The ears and nose were normal. Slight to moderate stiffness of the neck was present. Examination of the heart and lungs was normal.

Some muscle guarding was observed in the abdomen, but there were no masses or organs palpable and the abdomen was non-tender. There were no palpable lymph nodes. The cranial nerves were normal. The knee and ankle tendon reflexes were unusually brisk but symmetrical. A Babinski sign was thought to be present on the left side. Frequent muscle contractions were noted in the legs. The skin was warm but no lesions were present.

Laboratory Studies

Hemoglobin on admission was 14.2 grams; white blood count 5,900 with 79% neutrophils and 21% lymphocytes. Platelet count was 150,000. The urine had a specific gravity of 1.022 with no albumin or sugar, and contained 40 to 60 red blood cells and 25 to 30 white blood cells per high power field. Serum sodium was 140, potassium 3.4, chloride 96 and CO_2 23 mEq/L. Total serum protein was 6.1 gm%, of which 3.7 gm% was albumin. Serum calcium was 8.9 mg%, alkaline phosphatase 17 King-Armstrong units, bilirubin 0.8 mg%, BUN 15 mg%, blood glucose 100 mg% , SGOT 23 units. The heterophile test was negative. The cerebrospinal fluid was clear and colorless; it contained two cells, both mononuclears. Its protein content

was 54 mg%, its sugar 78 mg%. An India ink preparation was negative, as was a stain for acid-fast bacilli. Gram stain of the cerebrospinal fluid was also negative. A chest roentgenogram was normal.

Progress

The patient was given aspirin and an injection of chlorpromazine. The following morning his temperature was 102.8 degrees. He was lethargic and slightly confused. He still had generalized muscle aching and pains in the joints of his hands and feet. A petechial rash was now observed over his entire body including the palms of the hands and the soles of the feet. A Gram-stained smear made from one of these lesions was negative. Vomiting recurred several times and his headache remained severe. Serum fibrinogen was measured and found to be 0.21 gm%. Seventeen hours after admission the rash was becoming increasingly blotchy and extensive and the patient's sensorium was more obtunded. At this point further diagnostic procedures were performed.

Clinical Discussion

Dr. Robert Gruninger:*

The protocol describes the patient to a certain point where further clinical tests were necessary to make a definitive diagnosis. I do not know what these tests were but hope to suggest what they might or should have been. Nor do I know the course of the subsequent events, but I hope to predict what that course could have been on the basis of the suggested laboratory tests. My objective is to arrive at a tentative diagnosis so that we might suggest further diagnostic tests.

First, I would like to review certain salient points and relate them to the disease process that affected this 22-year-old draftsman. He was admitted with an acute illness characterized by severe frontal headache, vomiting, fever and muscle pain. His past history is significant in that certain possibilities need to be considered. First of all, he had poliomyelitis as a child with apparently complete recovery. One year prior to admission, he had what was described as an attack similar to the present illness, characterized by fever, headache and neck stiffness. Spinal fluid at that time was negative. However, the white count was elevated. He was hospitalized elsewhere for five days with a diagnosis of flu-like syndrome. He presented here with headache, vomiting and muscle pain. There is considerable emphasis on the muscle pain in the protocol, but I am not sure how important this was. Significant physical findings revealed an elevated temperature, a tachycardia and some questionable neck stiffness. The knee and ankle jerks were brisk and there was a questionable Babinski. Muscle contractures were noted but not further defined. I would suggest that these represented fasciculations. However, there were no muscle findings to suggest tetany, spasm, or trismus. The fact that the skin was clear on admission is an important observation. Laboratory studies revealed that there was no anemia. The total white count is perhaps of interest in that there were 5,900 WBC with 79% neutrophils. Platelets were 150,000 which, I believe, we should consider on the low side. The findings in the urine disclosed significant numbers of red and white cells. The heterophile was negative and the BUN, SGOT, bilirubin and glucose were normal. Initially the spinal fluid was clear and only two monocytes were seen. Chest x-ray was normal.

I am sure that the clinician at this time, in spite of normal cerebrospinal fluid findings, thought that this patient might have an acute meningitis. He was initially treated with aspirin and chlorpromazine, but his temperature remained elevated. Two important events ensued. He developed petechiae over the entire body which progressed to confluent purpura and ecchymoses. Furthermore, he developed central nervous system changes evidenced by con-

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fusion and lethargy. He still complained of severe headache and muscular pain. Thus further diagnostic tests were performed.

With this background, I would like next to consider what systems or general areas may be involved. His acute and fulminating course might possibly suggest a metabolic disease, possibly thyrotoxicosis, but there appears to be no supporting evidence. Could this be a cardiovascular disease? The purpura would be consistent with an endocarditis and septicemia; however, there is no history or findings suggestive of a cardiac lesion. I could not suggest pulmonary disease in the absence of a positive history and in the presence of a normal chest x-ray. In addition, renal disease might be considered; however, the urine findings were nonspecific and the presence of a normal BUN would seem to exclude a primary renal disease.

Central Nervous System

The events, however, do strongly suggest that he had primary involvement of the central nervous system. Meningitis was undoubtedly considered by the clinicians, though initially one could not say that he had a suppurative meningitis on the basis of the normal cerebrospinal fluid. There are some diagnostic tests that I would consider of additional importance; the first would be a repeat of the cerebrospinal fluid examination. His deep tendon reflexes were brisk but probably nonspecific; however, these could point to a central nervous system disorder. There was a questionable Babinski which probably was not of significance. Frequent muscle contractions were noted, and I would like to think that these were fasciculations. Some patients with polio may have fasciculations; possibly these could be some residual detected on the current admission. I would think that polymyositis and thyrotoxic or other myopathy could be excluded on the basis of the history and clinical findings. But with the progressive central nervous system symptoms I cannot exclude several processes, particularly a brain abscess.

Hematologic Process

Also I must consider a hematologic process, particularly with the progressive petechiae and purpura. This opens a whole new range of possibilities. For example, one might consider the nonthrombocytopenic purpuras which could include chronic renal disease, infections and allergic phenomena. Or this could be a thrombocytopenic purpura and, though I do not know what subsequent platelet counts showed, I would suggest that thrombocytopenia probably did occur. The various conditions giving rise to thrombocytopenic purpura raise a number of different possibilities. There are the essential or idiopathic variety and the symptomatic form which may be secondary to chemicals, toxins, medications, snake venom, x-rays, burns and other agents, none of which can be implicated in this particular case. There was no anemia or adenopathy to suggest or implicate another blood dyscrasia. Thrombotic thrombocytopenic purpura or Moschowitz syndrome is more frequently observed in women and is usually associated with a hemolytic anemia, not present in this particular case.

A variety of infections may cause this condition. Septicemia, either gram-negative or positive, subacute bacterial endocarditis, typhus, infectious mononucleosis, measles, and vaccinia have been implicated. Furthermore, fungus disease may induce low platelets; however, these are usually associated with diabetes, chemotherapy, or chronic lung disease. Collagen diseases raise a

whole new spectrum and cannot be entirely excluded; nevertheless, these were not suggested by the patient's history. Sarcoidosis and innumerable other conditions have also been implicated but do not appear to be factors in this case.

Intravascular Coagulating Syndrome

I would, however, like to invoke the intravascular coagulation syndrome. This syndrome remains a good possibility. There are a number of infectious diseases associated with it; in particular meningococcemia comes to mind. This certainly was suspected clinically as material was obtained from the skin lesion for microscopic examination; but this was negative for gram-negative diplococci. This fact, however, does not exclude such a diagnosis. Other bacteremias may result in a consumptive coagulopathy; *E. coli,* hemolytic Streptococcus, Staphylococcus, and Pseudomonas have been implicated. None of the aforementioned viral infections, however, seem to fit this case.

Meningococcemia

I would like to believe that this man had a septicemia, probably meningococcemia, and because of this developed the intravascular coagulation syndrome. Thus a number of additional diagnostic tests are indicated. A blood culture and repeat spinal fluid would be very helpful. In evaluation of the intravascular coagulation syndrome, a repeat platelet count and observation of clot formation are important. Furthermore, the clotting time and the prothrombin time should be considered; both would be prolonged. In addition, fibrinogen assay, partial thromboplastin and thromboplastin generation tests may be of additional value. There are at least three acceptable methods for fibrinogen determinations, and I would expect the values of these to be quite low in a consumptive coagulopathy. In addition, there are certain clotting factors, namely, factors V and VIII which should be considered; but of course these are generally not practical in an acutely ill patient with a fulminating course. In addition, fibrinolysis may be evident and could be evaluated with the euglobulin lysis test.

Some of these tests are not practical, as mentioned, and I would consider the four most important determinations in evaluation of consumptive coagulopathy to be the platelet count, the clotting time, the prothrombin time and the fibrinogen level. If these are abnormal, then a presumptive diagnosis of intravascular coagulation can be made, and I would then institute heparin therapy. The cause should then be determined. I must re-emphasize that a blood culture is indicated, but the results could take several days.

The one entity I cannot exclude is that of a brain abscess with septicemia. The initial symptoms one year before are quite consistent with the acute cerebritis associated with a brain abscess. These may present as a flu-like syndrome but then usually become quiescent; and it would seem unlikely that these would then present with an acute fulminating course in the absence of cerebrospinal fluid findings. I would like to think that this patient did have a flu-like syndrome a year ago rather than a cerebritis with secondary brain abscess. Certain diagnostic tests would be helpful in evaluating a brain abscess, namely, an electroencephalogram, and angiograms. Though I cannot exclude a brain abscess as a possibility, I believe that this patient had a fulminant meningococcemia, probably without meningitis, and secondary to this, the intravascular coagulation syndrome.

Comments

Dr. Robert Strom:*

Would you consider or exclude the Rickettsial diseases, particularly Rocky Mountain spotted fever, in this instance.

Dr. Gruninger:

I do not believe this patient had Rocky Mountain spotted fever for several reasons. We do not have a history of traveling in endemic areas, there is no documentation of a tick bite, and initially this lesion resembles a flea bite though ultimately it may become generalized and purpuric. Though this patient developed a rash while in the hospital, an initial tick bite is not described. Furthermore, Rocky Mountain spotted fever may be fulminating but is usually not as rapidly progressive as in this instance.

A Medical Student:

At what stage in this man's illness would you have instituted therapy.

Dr. Gruninger:

Initial laboratory findings of low platelets and low normal fibrinogen were suggestive of the intravascular coagulation syndrome. If additional coagulation studies, as already mentioned, were confirmatory, I would have instituted heparin therapy. Furthermore, with a presumptive diagnosis of meningococcemia and once a blood culture had been drawn, I would have begun penicillin treatment. This is now the drug of choice due to the increasing numbers of infections by group B organisms. Many are resistant to the sulfonamides.

Clinical Diagnoses

1. Fulminant meningococcemia
2. Intravascular coagulation syndrome

Pathology Discussion

Dr. Robert Anderson:*

Dr. Gruninger has presented a very complete analysis of the diagnostic problems presented by this patient and is entirely accurate in his interpretation of the events that transpired. This patient did succumb to a fulminant meningococcemia, and we are particularly interested in presenting this case not only because the histopathologic lesions are quite characteristic of those encountered in meningococcemia; but, furthermore, they are supportive of some of the more recent concepts in the pathogenesis of this entity.

Neisseria Meningitidis

The diagnosis was confirmed by cultures of both blood and cerebrospinal fluid which yielded Neisseria meningitidis. Furthermore, serotyping revealed the organism to be Group B. A further bit of confirmatory evidence was the presence of characteristic gram-negative diplococci within neutrophils present in smears of cerebrospinal fluid exudate obtained prior to death.

Meningococcemia

At necropsy his external appearance was quite typical for meningococcemia. There were numerous petechiae, ecchymoses and confluent purpura present

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over the trunk and extremities, with a predisposition for the latter areas. The head and neck were relatively spared. Furthermore, there were numerous petechiae and ecchymoses over serosal membranes, particularly prominent over both pleural surfaces, and to a lesser extent over the epicardium. Occasional petechiae were also present over peritoneal surfaces and the leptomeninges.

The brain was one of the tissues of prime interest. Upon removal of the calvarium, there was an obvious diffuse milkiness of meninges over the convexities. This exudate was concentrated in sulci resulting in accentuation of cortical vessels. There was a moderately heavy purulent exudate at the base of the brain, extending over the inferior temporal lobes and the inferior surface of the cerebellum. On sectioning, the white and grey matter were spared; however, there was an exudative thickening of the meninges. Histologic examination showed an acute purulent meningitis characterized by extensive neutrophilic infiltrate of leptomeninges (Figure 1). The white matter was uninvolved and the cortex showed only occasional leucocytic margination of small cortical vessels.

Terminal failure was undoubtedly reflected in the marked bilateral hydrothorax and pulmonary edema. Both pleural cavities contained approximately one liter of blood-tinged fluid. The lungs were massively edematous and together weighed 2700 grams. Sections disclosed widespread edema and marked congestion, but no sites of pneumonitis.

The adrenal glands were perfectly normal. There was no evidence of hemorrhage, necrosis or cortical lipid depletion. Microscopically, the only change of note was the presence of a pseudotubular degeneration, a nonspecific finding not infrequently present in overwhelming infectious states. The abdominal viscera were congested but otherwise normal, and the kidneys were not remarkable.

The heart was the site of a fairly striking myocarditis. Although this has been observed with some frequency in meningococcemia, the pathogenesis

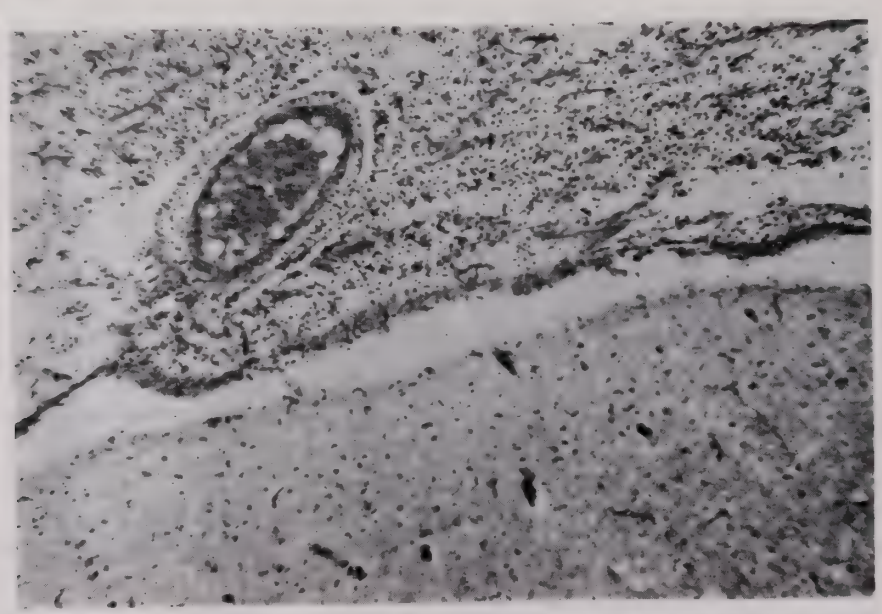


Fig. 1—A representative section from the cerebral convexities discloses extensive acute purulent meningitis.
Hematoxylin and eosin. ×100

and histopathology of these lesions have received little attention. Generally, the infiltrate was present in two areas: predominantly perivascular in location and to a lesser extent in and around myofibers. The perivascular infiltrates were polymorphous in nature and comprised principally of polymorphs together with increased numbers of Anitschkow myocytes, the counterpart of the reticulum cell in the heart (Figure 2). This latter change might suggest some injury or stimulation of the reticuloendothelial system. Furthermore, vessels in the area of the inflammation showed increased prominence and swelling of endothelial cells, perhaps indicative of endotoxin-induced

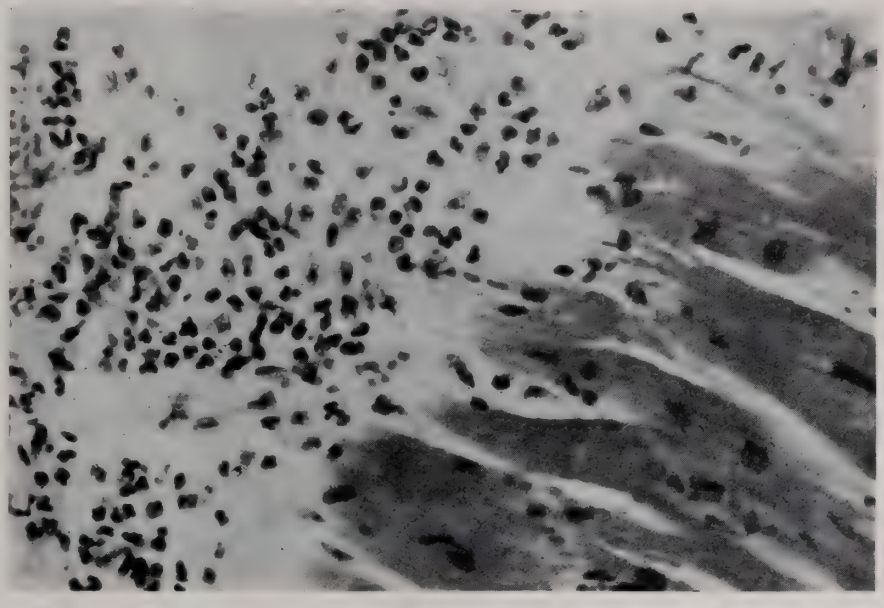


Fig. 2—Acute interstitial myocarditis in which a fairly extensive neutrophilic infiltration is interspersed with a few monocytes and Anitschkow myocytes.
Hematoxylin and eosin. ×200

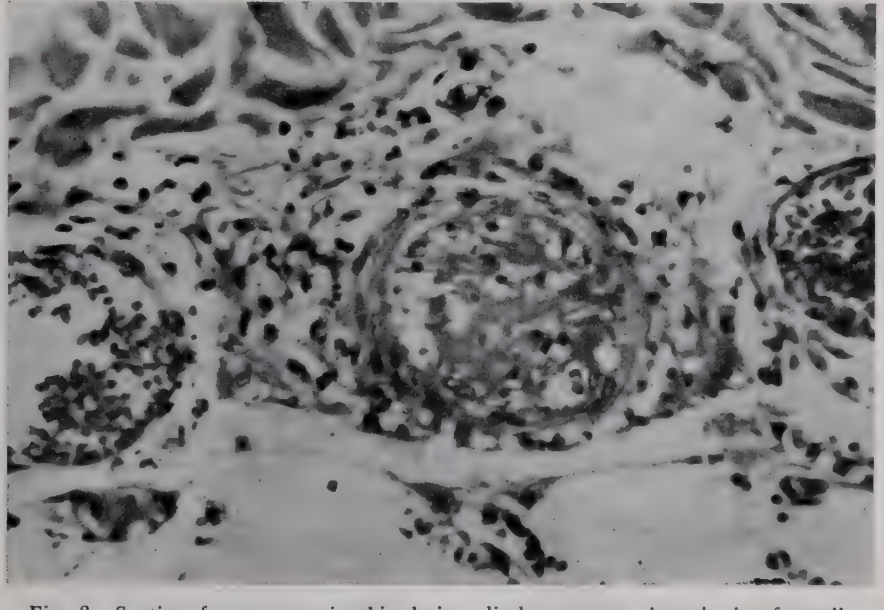


Fig. 3—Section from purpuric skin lesion discloses acute thrombosis of small dermal arteriole associated with an acute vasculitis.
Hematoxylin and eosin. ×200

injury. Myofibers for the most part were well preserved, though some did show necrobiotic changes characterized by either nuclear pyknosis or occasional foci of cytomyolysis, a change possibly secondary to endotoxin-induced injury.

Vascular changes in small vessels of the skin were of considerable interest and illustrative of those stages of vascular damage that have been described in meningococcemia. The earlier changes are characterized by endothelial swelling, fragmentation, desquamation of endothelial cells and sludging of red cells. Meningococci have been identified within endothelial cells in this stage, though they were not evident in this instance. The latter stages of injury are characterized by polymorphs infiltrating damaged endothelium, the vessel wall, and the perivascular tissues. An acute vasculitis as well as necrosis of vessel wall may occur. Of particular note is the development of platelet and fibrin thrombi at this stage, which may become quite widespread and which was readily evident in this patient (Figure 3).

These stages of vascular damage were well documented in a study approximately 20 years ago by Drs. Hill and Kinney. It was their concept that the initiating insult was the localization of meningococci within the endothelial cells with subsequent inflammation and vascular damage. However, it has been observed in subsequent studies that meningococci are infrequently found in endothelial cells, as was true in this case. Many authorities now believe that these changes within small vessels of the skin and subcutaneous tissues represent multiple local Shwartzman reactions in which skin sites become prepared by endotoxin in the early bacteremia phase, with the provocative phase occurring later from the continuing bacteremia. Similar changes with extensive sinusoidal thrombosis are often present in the adrenal glands. This endocrine is now also considered to be a site for the Shwartzman reaction, and some investigators suggest that this phenomenon is the precursor of adrenal hemorrhage and necrosis characteristic of the Waterhouse-Friderichsen syndrome. Glomerular capillary thrombi are also fairly common in meningococcemia, though they were not evident in this case. A few cases of renal cortical necrosis have recently been described in meningococcemia, and this would seemingly implicate a generalized Shwartzman reaction as an additive factor in the pathogenesis of meningococcemia in some instances.

Consumptive Coagulopathy

The extensive vascular changes with thrombosis also implicate a different process worthy of comment. Hill and Kinney in their study emphasized the purpuric nature of meningococcemia and considered it to be directly related to the widespread vessel thrombosis with depletion of circulating platelets. They described the syndrome of consumptive coagulopathy though they did not coin this term. The frequent occurrence of this syndrome in patients with meningococcemia has been clearly established, and it is thought to be initiated by the Shwartzman reaction. The patient under consideration today did suggest an early consumptive coagulopathy evident by hemorrhagic tendency, diminished platelets, and prolonged prothrombin time. Small-vessel thrombosis can be quite widespread and is usually evident in vessels of the skin and subcutaneous tissue, the kidneys, adrenals, pancreas and lungs to a lesser extent. One site frequently overlooked is the choroid plexus. I have had the opportunity to study several cases of meningococcemia, and in all of these, including this present case, the choroid plexus was the site of numerous small vascular thrombi. In conclusion, this young male succumbed to ful-

minant meningococcemia. The histopathologic lesions were quite characteristic of those seen and are supportive of the concept that an interaction of endotoxinemia, multiple Shwartzman reactions, and consumptive coagulopathy is of prime importance in the pathogenesis of this entity.

Pathological Diagnoses

1. Fulminant meningococcemia with acute purulent meningitis
2. Intravascular coagulation syndrome

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Erratum

The June* issue of MINNESOTA MEDICINE contained a short biography of Joseph N. Gehlen, M.D., in recognition of his 50 years of distinguished service in the practice of medicine. The Board of Editors wishes to correct this biography as follows:

> JOSEPH N. GEHLEN, M.D., St. Paul, Minnesota . . . specialized in internal medicine and obtained his medical education at Creighton University at Omaha, Nebraska; he was graduated in 1918. Earlier, he had received his B.S. degree from St. Martins College in Olympia, Washington. He interned at Lord Lister Hospital in Omaha, the U.S. Naval Hospital in Newport, Rhode Island and St. Mary's Hospital in Providence, Rhode Island. He practiced from 1919 to 1920 in LeMars, Iowa, his native community. After coming to Minnesota, he did post-graduate work at the University of Minnesota and became epidemiologist for the Minnesota State Board of Health. He began practice in St. Paul in 1925 and has served on the staffs of Ancker, Miller, St. Joseph's and St. Luke's Hospitals. He was chief of the tuberculosis service at Ancker Hospital from 1939 to 1958. He is a member of the American College of Chest Surgeons, the American Society of Internal Medicine and the Trudeau Society.

*See page 808.



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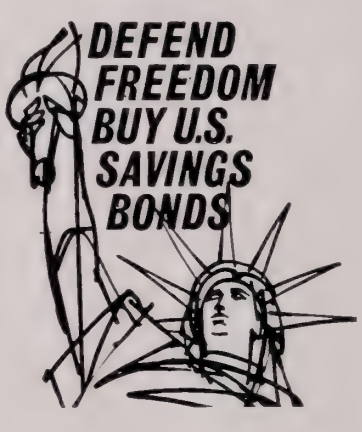
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Review—

The Metabolic Effects of the Periwinkle Alkaloid Vinblastine

VINBLASTINE IS an extract of the plant *Vinca rosea Linn* (periwinkle). It was first isolated as the sulfate salt by Noble, Beer, and Cutts[15] at the University of Western Ontario. The characterization was carried out by Neuss et al.[11,12,13] at the Lilly Laboratories. This latter group found it to be a complex molecule, containing both an indole and indoline moiety. The indole portion is related to catharanthine, whereas the indoline portion is related to vindoline. Thus, in essence, it is a non-symmetrical dimeric alkaloid (Figure 1). Clinically vinblastine finds use in the treatment of Hodgkin's disease and also in the treatment of choriocarcinoma.

Physical Values

Vinblastine is a dimeric alkaloid which contains both an indole and indoline moiety. It has two pk^a values, 5.4 and 7.4 (in H_2O). Maximum ultraviolet absorptions are at 214 and 259 mu. It is dextrorotatory with $(\alpha)^{26}$ $CHCl_3$ equal to +72, and has a melting point (decomposition) of 211-216°C.[8]

Structure and Activity

Vinblastine no longer produces its biologic effect if the structure of the vinblastine molecule is altered in relatively minor ways[14] (Figure 2).

The Dimer VLB and Its Parent Monomers

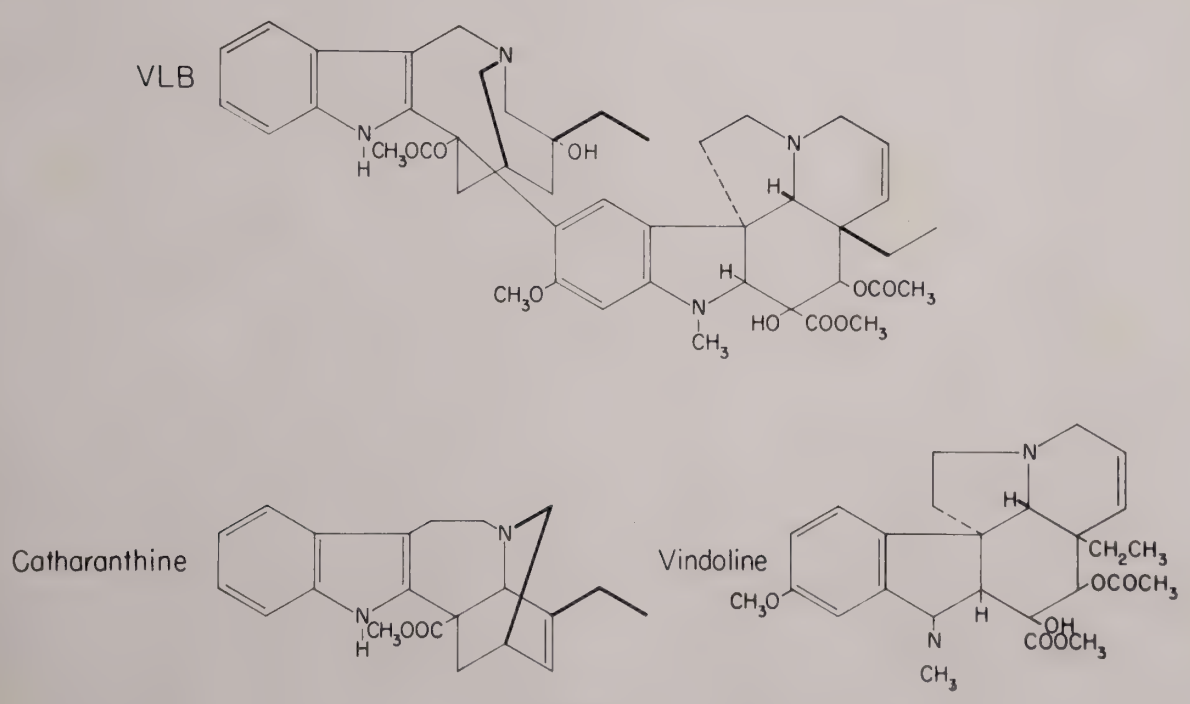


Figure 1

That such small structural changes are important in determining anti-tumor effect can be seen from the fact that few other alkaloids derived from the periwinkle plant are active anti-tumor agents. Those that are, e.g., vincristine, differ quantitatively and qualitatively in their effects.

It is no easy matter to account for differences in biologic action with slight molecular changes but there are a number of explanations that come to mind:

1. A reactive site may be altered by chemical combination, as in amidization or quaternization of the indole nitrogen of vinblastine.
2. Addition of groups may result in steric hindrance of reactions, as in the acetylation of the hydroxyl groups of vinblastine, particularly if vinblastine, or a metabolic product of vinblastine, interferes with an enzyme system.
3. Changes in charge distribution may affect the reactivity of vinblastine, as in the hydrogenation of double bonds.

All of the above explanations hold for enzymic and non-enzymic mechanisms, in the former case because of direct changes in reactivity, in the latter case because of structural changes as well.

Finally, it should be remembered that a structural change may hinder the metabolism of a compound more or less severely, or it may make for a different product of metabolism, which may or may not be active.

Metabolism of Vinblastine

In studies conducted by Beer et al.[1] in which vinblastine was labeled with tritium by the Wilzbach irradiation method, it was found that some 5% of dose radioactivity was excreted in the urine over a 26-hour period following injection of the drug into rats. Two per cent of this amount appeared in the urine within the first three hours. After the same 26-hour time interval, 1 ml. of blood contained 0.08 ± 0.01% of the injected radioactivity, or approximately 1.2 ± 0.15% of the dose in terms of total blood volume. In an additional study, Beer et al.[2] reported results in agreement with the above. This second study included dose-radioactivity for a number of organs (Table). It is interesting to note that some 25% of dose-radioactivity from labeled vinblastine is excreted via the gut, and together with the excretion in the urine, nearly one third of the dose leaves the rat by these routes. Of the remaining two thirds, only 2.0% is left unchanged by the liver.

It remains to be seen whether the activity of the liver enhances or decreases the effect of vinblastine. It is known, however, that the intraperitoneal dose for the LD50 in mice is much less than the intravenous dose (3.2 mg/kg vs. 17.5 mg/kg) and that the oral dose is

TABLE[a] 1.

Tissue distribution of radioactivity in a rat 24 hours after the injection of tritiated vinblastine

Tissue, organ, etc.	Total wet wt. of tissue mg.	Radioactivity of fresh tissue cpm/mg.	Total cpm. in tissue	% of injected radioactivity[b]
Liver	6800	4.4	29920	2.88
Kidneys	1500	2.5	3750	0.36
Spleen	640	6.0	3840	0.37
Thymus	190	3.5	665	0.06
Brain	2400	0.55	1320	0.13
Bone marrow	———[c]	3.0	———	———
Muscle	———[c]	2.0	———	———
Intestine	4100	3.3	13530	1.30
Intestinal contents	———	———	254760	24.50
Blood	14900[d]	1.1	16390	1.58
Urine[e]	———	———	68970	6.63

[a]Table reproduced from *Can J Physiol Pharmacol* 42:368 1964 by permission.

[b]Vinblastine (1,040,000 cpm) injected into the tail vein.

[c]Total bone marrow and muscle weights not available.

[d]Blood weight was assumed to be 7.5% of total body weight (199 g).

[e]0-24 hr urine; collected as one sample.

higher than either (33.1 mg/kg).* This would indicate two things: (1) the liver probably modifies the drug, and (2) stomach acidity inactivates the drug, or prevents absorption.

In an experiment carried out by the author,† no change in the ultraviolet spectrogram of vinblastine appeared after incubating the drug at 37°C and pH 7.4 for six hours in an attempt to simulate body environment in terms of physical parameters. Four mg of vinblastine was dissolved in 50 ml. of phosphate buffer in a glass test tube. The tube was placed in a 37°C water bath and mechanically shaken throughout the six hours of the experiment time. The ultraviolet spectrogram was done on the buffer solution.

The absence of change in the spectrogram indicates that body pH and temperature *per se* do not alter drug configuration so far as ultraviolet analysis can show.

Vinblastine and Cell Respiration‡

In studies carried out by Katchman et al.,[19] the metabolism of human cancer cells as modified by drug action was measured in terms of three parameters:

1. Oxygen uptake as a measure of respiratory activity,
2. Formation of lactic acid as a measure of aerobic fermentation, and
3. Glucose disappearance or utilization as a measure of total carbohydrate metabolic potential. Only the effect of vinblastine will be reported here.

*Data from Eli Lilly Company.
†Unpublished data.
‡Experimental data in this section from Katchman et al; See original paper for discussion of technique and drugs used.

Structural Modifications of VLB which are Biologically Inactive

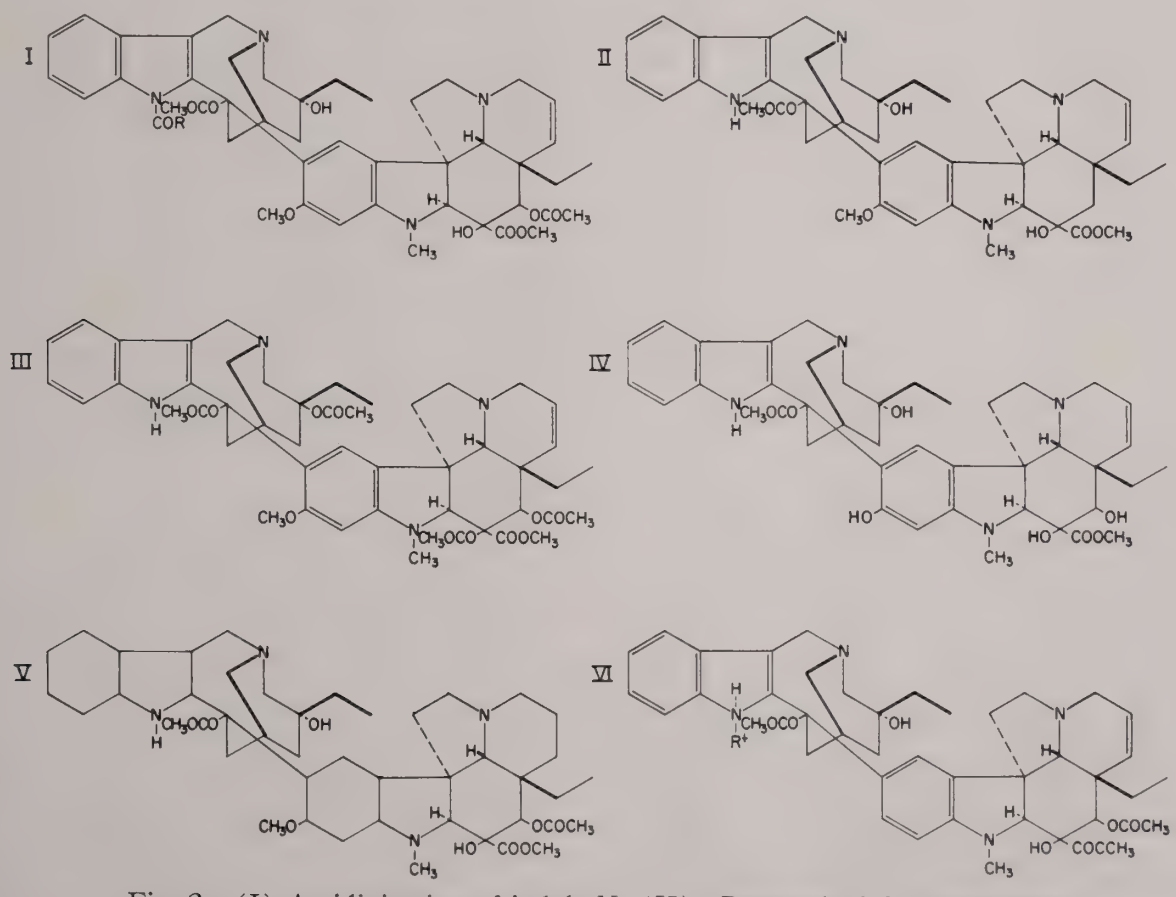


Fig. 2—(I) Amidinization of indole N. (II). Removal of C_4 acetyl group of vindoline moiety. (III) Acetylation of hydroxyls. (IV) Reduction with $LiAlH_4$. (V) Hydrogenation of double bonds. (VI) Quaternization of indole N.

Oxygen Uptake

When vinblastine is added to a suspension of human cancer cells (leukemia), the effect of the drug is to decrease oxygen uptake. This effect of vinblastine on cell respiration as measured by oxygen uptake is greater than for other common anti-cancer drugs. This correlates with the severity of leucocytopenia produced by the drug. Vinblastine reduces oxygen uptake from 49 ml/hr. to 34 ml/hr. over a 90-minute test period and at a dose of 3.3 mcg/10^6 cells. This represents a 30% reduction in uptake of O_2 (Figure 2).

Lactic Acid

Cancer cells produce lactic acid even while in the presence of O_2.* When vinblastine is added to a suspension of cancer cells, lactic acid production is increased above normal values from 0.44 mg. to 1.00 mg. over a period of 190 minutes and with a concentration of vinblastine of 3.6 mcg/10^6 cells. Again, the effect of vinblastine is greater than for other chemicals studied.

*These cells also exhibit the Crabtree effect. When glucose is added to these cells, O_2 uptake decreases.

Effect of VLB on Cell Energy Metabolism
(After Katchman, et al)

	Lactic Acid
Control	0.44 mg
VLB	1.00 mg
% Control	227

222 x 10^6 Cells at [VLB] of 3.6 µg/10^6 Cells for 190 min with Glucose in Cell Suspension

	O_2
Control	49 µl
VLB	34 µl
% Control	69

230 x 10^6 Cells at [VLB] of 3.3 µg/10^6 Cells with Glucose in Cell Suspension

	Glucose
Control	0.20 mg
VLB	0.60 mg
% Control	300

3.3 µg/10^6 Cells

Figure 3

Glucose

Glucose utilization by cancer cells in the presence of vinblastine (3.3 mcg/10^6 cells) increases from the control value of 0.2 mg. to 0.6 mg. Essentially all glucose can be accounted for as glucose equivalents used in respiration and lactic acid production. This fact, coupled with the observation that at sufficiently low concentrations vinblastine does not inhibit respiration, makes the agent a true Pasteur effect inhibitor; i.e., it stimulates lactic acid production without inhibition of respiration (Figure 3).

Vinblastine and Nucleic Acid Metabolism

Richards and Beer[16] studied the effect of vinblastine on nucleic acid synthesis using 14C-Formate. The following results were obtained:

1. Nucleic acid synthesis was depressed.
2. Desoxyribonucleic acid synthesis was depressed more than ribonucleic acid synthesis.
3. Desoxyribonucleic acid-adenine and desoxyribonucleic acid-guanine were decreased below control levels to a greater extent than desoxyribonucleic acid-thymine.

Richards and Beer suggest two possible mechanisms for the inhibition of nucleic acid synthesis. Either there is interference with the polymerase reaction, or there is decreased synthesis of nucleotide precursors. They consider the latter possibility more likely in view of the differential effect on adenine and guanine vs. thymine synthesis. Also there is evidence that there is no interruption in synthesis of inosinic acid or of thymidylic acid.

Vinblastine and Mitosis

Vinblastine is a potent metaphase arrestor showing dosage effects comparable to those of colchicine and sometimes surpassing them. While the Syrian hamster proves resistant to colchicine, vinblastine produces complete metaphase arrest of Syrian hamster cells.[3] Unlike colchicine, the arrest is reversible by treatment with various amino acids, particularly glutamic acid. Although this is one of vinblastine's most striking properties, the stathmokinetic effect does not correlate well with antitumor activity of the drug.[7,17]

The appearance of the chromosomes of cells arrested in metaphase by vinblastine is that of the colchicine-mitosis pattern, where chromosomes are clumped, shortened, and paired. The nuclei are pyknotic and take the form of the ball mitosis. Occasionally exploded metaphases are seen.[3,4,5,17]

Vinblastine and Amino Acids

Johnson et al.,[7] by adding various amino acids to vinblastine treated systems, found that the effect of vinblastine was considerably reduced.[7] This effect was seen at low doses of vinblastine. With higher doses, amino acids had no effect. The compound found to be most effective in this respect is L-glutamic acid.

Vinblastine and Prophage-Inducing Action

Endo et al.[6] have reported that certain chemotherapeutic agents have prophage-inducing ability that correlates well with tumoricidal action of the agents. Endo and colleagues observed induction of lysogenic bacteria with mitomycin C and various of its N-substituted derivatives where the substituting group is an alcohol. Vinblastine failed to show any such action.

Discussion

The metabolic effects of vinblastine suggest possible correlations between its effects on respiration and its effects on nucleic acid synthesis. Vinblastine has an effect both on the oxygen uptake of cells and on their production of lactic acid. It affects the utilization of glucose as well. In addition, it apparently reduces the synthesis of nucleic acids, probably by interfering with the formation of nucleotides.

A possible explanation for the increased lactic acid production and increased utilization of glucose is suggested by the fact that vinblastine interferes with nucleotide formation; that is, the inhibition of nucleotide synthesis causes a shortage of the cells' energy-storing compounds, particularly adenosine diphosphate. Consequently the cells revert to glycolytic respiration, the metabolism of glucose goes up, and the output of lactic acid rises. Along with these changes, oxygen use falls.

Simply then, the observation that more glucose is metabolized, more lactic acid is produced, and less oxygen is used up constitutes evidence that the cells have reverted to aerobic fermentation with the less efficient energy production per glucose molecule. Such reversion ordinarily occurs in anoxia of tissues and is seen in shock as it progresses to irreversibility. The cells however were not anoxic in the experiments of Katchman et al.,[19] which leads one to suppose that the trichloroacetic acid cycle is partially inoperative for reasons other than oxygen lack.

The fact that cancer cells normally produce lactic acid in the presence of oxygen would seem to suggest that their energy manufacturing mechanisms are already suffering from malfunction. Alternatively, the mechanism is working at full capacity, so that adenosine diphosphate becomes scarce, and additional energy is supplied glycolytically.* In consequence, any agent which selectively attacks the energy-forming mechanisms produces a favorable anti-tumor response over and above damage to normal cells. This then could explain the greater susceptibility of certain cancer cells to vinblastine.

It has already been stated (v.s.) that there is no straight-forward correlation between the stathmokinetic and the anti-tumor effects of vinblastine. Thus it would seem that anti-tumor action is achieved primarily by making an already inefficient mode of energy production even more so to the point of causing cell death by a mechanism other than simple mitotic arrest and interphase "death." Tumor cells by this hypothesis are "energy-starved" in relation to other cells. Tumors that are less metabolically active are likely to respond more like normal cells to vinblastine.

This may not be the only reason vinblastine has a pronounced action on some cells and not on others. Quite possibly some of the differential action can be explained enzymatically. It is possible that enzymes differ according to stem cell type and that while reticuloendothelial cells are affected, nerve cells are not, because a particular enzyme or enzymes, due to structural characteristics, can be affected by vinblastine in the first case and not in the

*The cells are metabolizing so rapidly that they utilize the faster energy-forming glycolytic sequence to maintain their rate. The Crabtree effect would support this idea.

second*.

If the effect is one of enzyme competition, it is likely to involve nucleotide precursors after and including inosinic acid (Richards and Beer). It is possibly competitive because the drug has an increasing effect with increasing dose.

As for the effects of glutamic acid, these can be explained by postulating that vinblastine is a competitor of inosinic acid, or a competitor of a product of inosinic acid leading to the nucleotides. By increasing glutamic acid, the amount of synthesized inosinic acid increases, and in effect, the acid becomes more competitive.

The Warburg Shift

Four decades ago, the biochemist Warburg postulated that respiratory injury is the cause of cancer, and pointed to the shift to aerobic fermentation exhibited by cancer cells.[18] It is apparent from the work of Katchman and his co-workers that vinblastine, and to a lesser extent other antitumor drugs, can be considered Warburg-shift agents. But what is most important, the action of vinblastine and these other drugs indicates that interference with nucleic acid chemistry is associated with the Warburg shift.

Conclusion

The anti-tumor effect of vinblastine may possibly be due to its effect on cell energy mechanisms. Adenosine diphosphate production is decreased by retarded nucleotide production. Its mitotic effects may also relate to retarded nucleotide production as may its action as a Warburg-shift producer. Its selective nature of action is possibly due to a number of factors (energy differences, enzyme differences, permeability differences). Finally, its therapeutic ratio may depend on the greater energy needs of cancer cells along with their decreased efficiency in generating energy because of their reliance on the glycolytic pathway. There may be dependence on glycolysis because of some inherent malfunction, or because of simple adenosine diphosphate shortage.

Thomas M. Cosgriff†
Minneapolis, Minnesota

*Alternatively, enzymes differ according to "housing" or to accessibility.

†Predoctoral Trainee, Division of Radiation Therapy, University of Minnesota Hospitals.

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References 9-18 may be secured from the author.

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Merchants National Bank and Trust Company of Fargo v. U.S., 272 F. Supp. 409 (D.C., N.D., Sept. 11, 1967; as corrected, Oct. 16, 1967).
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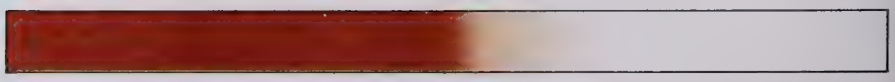
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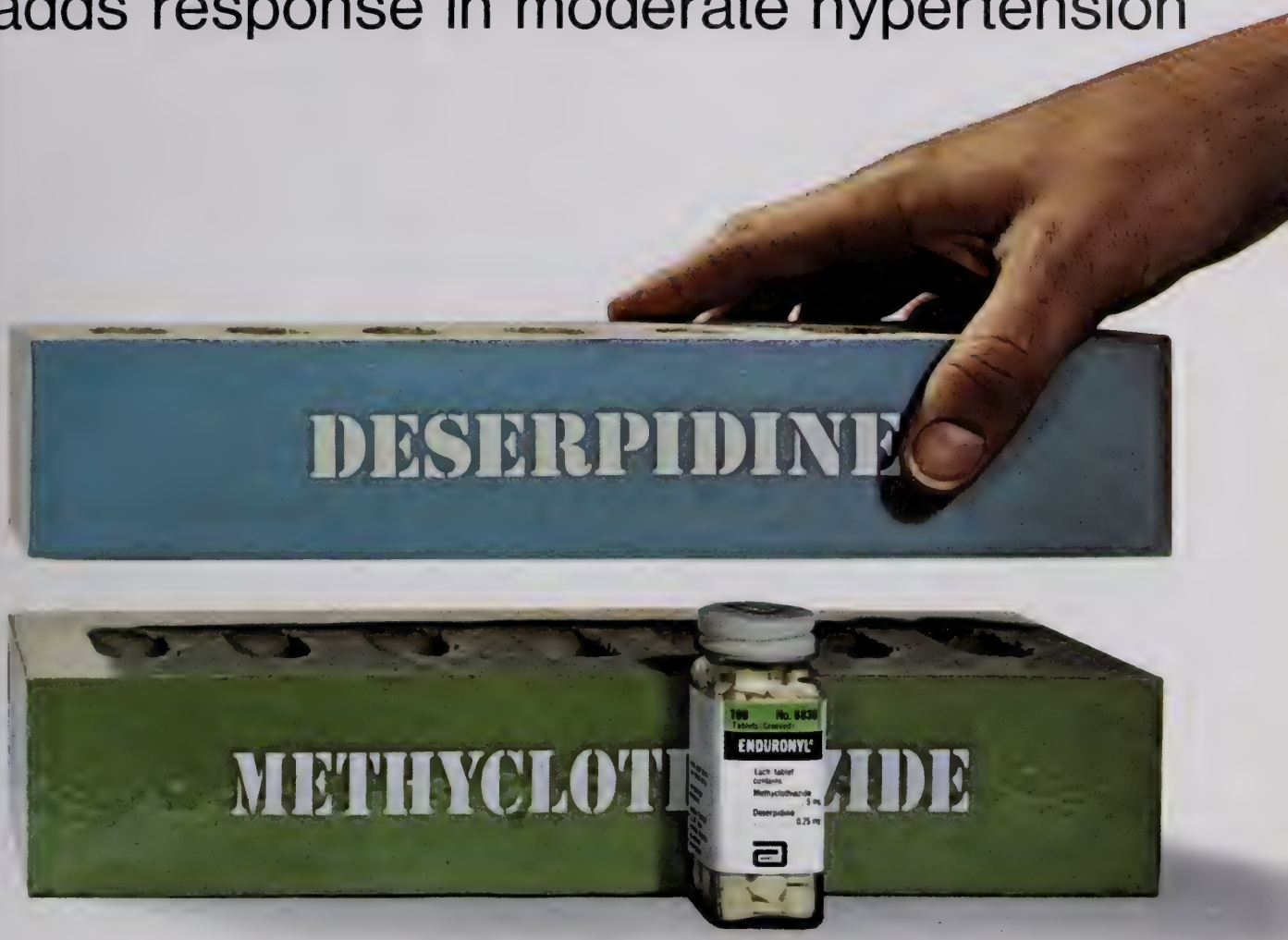
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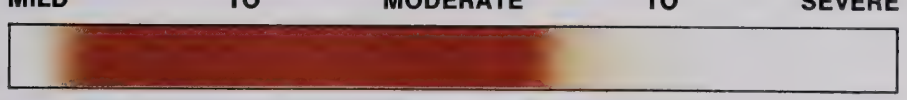
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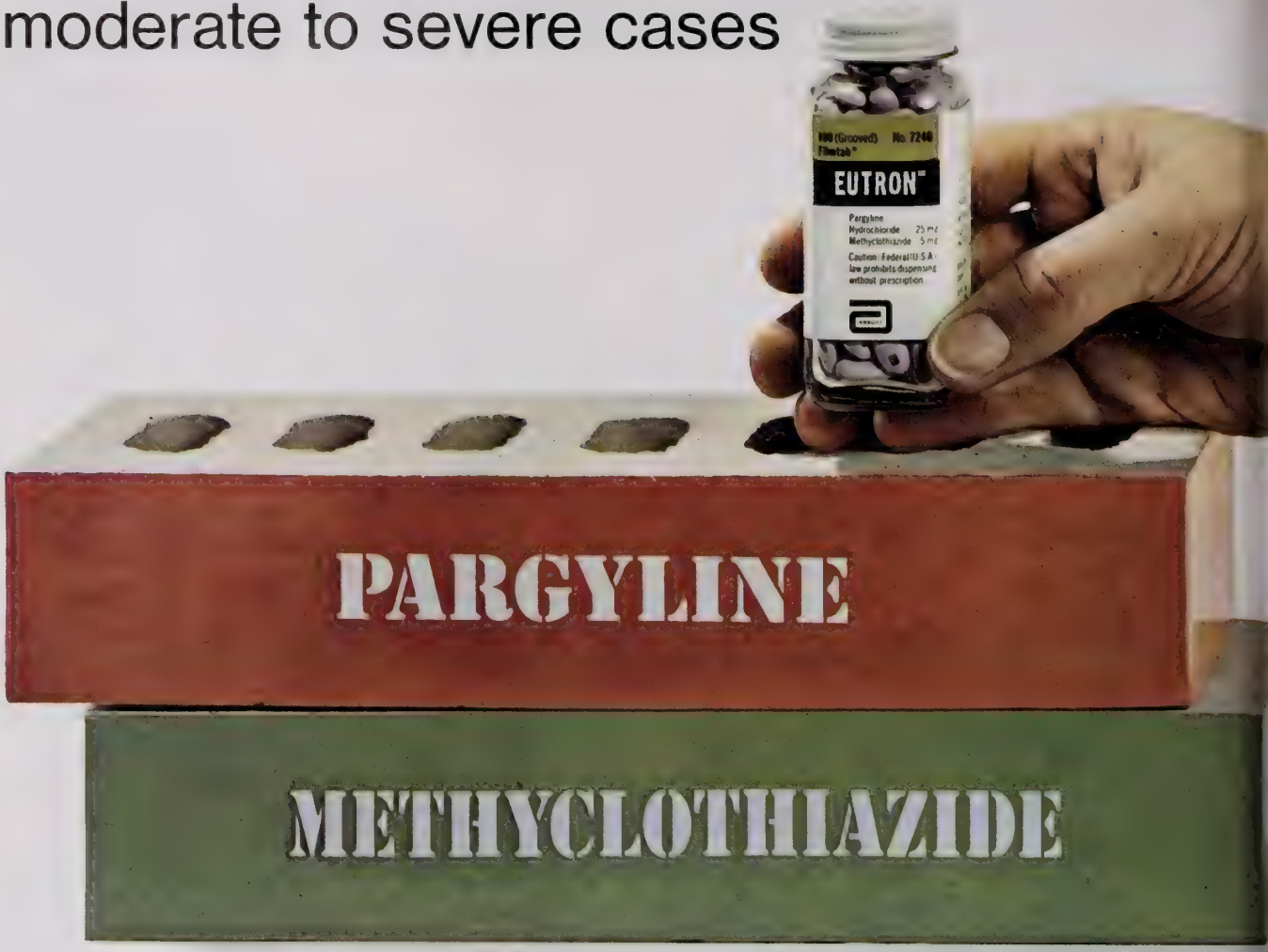
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Sensitivity to thiazides; severe renal disease (except nephrosis) or shutdown; severe hepatic disease; impending hepatic coma from thiazide-induced hypokalemia.

Warnings—Patients: 1. No other drugs (particularly "cold preparations" and antihistamines), cheese or alcohol without physician's consent. 2. Promptly report orthostatic symptoms, severe headache, other unusual symptoms. 3. Angina pectoris or coronary artery disease patients must not increase physical activity with improved anginal symptoms or well-being.

Physicians: 1. Use antihistamines, hypnotics, sedatives, tranquilizers and narcotics (meperidine contraindicated) cautiously in reduced doses. 2. Stop Eutron two or more weeks before elective surgery; in emergency surgery reduce premedication (narcotics, sedatives, analgesics, etc.) to 1/4 to 1/5; carefully adjust anesthetic dosage to patient response. 3. Use cautiously in advanced renal failure. 4. Pargyline may induce hypoglycemia. 5. Consider possible sensitivity reactions when a history of allergy or asthma is present. 6. If potassium is indicated, dietary supplement is recommended; enteric-coated potassium tablets may induce serious or fatal small bowel lesions (stenosis with or without ulceration), cause obstruction, hemorrhage, and perforation frequently requiring surgery; discontinue medication immediately if abdominal pain, distention, nausea, vomiting or gastrointestinal bleeding occurs; Eutron does not contain added potassium. 7. Possible systemic lupus erythematosus has been reported for thiazides.

Precautions—Pargyline: Use cautiously at reduced dosage: caffeine, alcohol, antihistamines, barbiturates, chloral hydrate, other hypnotics, sedatives, tranquilizers, narcotics. Periodically do urinalyses, blood counts, liver function tests, etc. Use with caution in liver disease. Watch for orthostatic hypotension, especially in impaired circulation (e.g., angina pectoris, coronary artery disease, cerebral arteriosclerosis); also, augmented hypotension in concomitant febrile illnesses. Reduce or discontinue if hypotension is severe. In impaired renal function watch for cumulative drug effects, elevated BUN and other evidence of progressive renal failure; withdraw drug if these persist. In surgery increased central depressant response (hypotension and increased sedative effect) can be controlled by (1) discontinuing at least two weeks prior; (2) in emergency surgery lowering dose of premedication; (3) when necessary, administering a vasopressor. Do not use in hyperactive and hyperexcitable patients. Pargyline may unmask severe psychotic symptoms where emotional problems pre-exist. Use cautiously in Parkinsonism, especially with antiparkinsonian agents. In prolonged therapy, examine for change in color perception, visual fields, fundi and visual acuity. Also, prolonged therapy has made certain patients refractory to nerve blocking effects of local anesthetics.

Methyclothiazide: Use cautiously in severe renal dysfunction, impaired hepatic function or progressive liver disease; also in pregnancy (bone marrow depression, thrombocytopenia, and altered carbohydrate metabolism have been reported in certain newborn). In surgery thiazide may reduce vasopressor response and increase tubocurarine response. Antihypertensive response may be enhanced following sympathectomy. Watch for electrolyte imbalance (e.g., hyponatremia). Give supplemental chloride if hypochloremic alkalosis occurs and supplemental potassium if hypokalemia occurs (especially in digitalized patients). Thiazides may decrease serum P.B.I. without signs of thyroid disturbance.

Adverse Reactions — Pargyline: Orthostatic hypotension and associated symptoms, mild constipation, fluid retention, edema, dry mouth, sweating, increased appetite, arthralgia, nausea, vomiting, headache, insomnia, difficult in micturition, nightmares, impotence, delayed ejaculation, rash, purpura, weight gain, hyperexcitability, increased neuromuscular activity and other extrapyramidal symptoms. Drug fever is extremely rare. Reduction in blood sugar and hypoglycemic effects are possible. Congestive heart failure has been reported in a few patients with reduced cardiac reserve.

Methyclothiazide: Blood dyscrasias (thrombocytopenia with purpura, agranulocytosis, aplastic anemia); elevation of BUN, blood sugar or serum uric acid (gout may be induced); anorexia, nausea, vomiting, diarrhea, headache, dizziness, paresthesia, weakness, skin rash, photosensitivity, jaundice and pancreatitis. Cutaneous vasculitis in elderly patients has been reported with other thiazides.

If side effects are severe or persist, reduce dosage or withdraw drug. 804438R

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Grand Rounds

Isoniazid Prophylaxis

OLE M. JERDE, M.D.
Minneapolis, Minnesota

"There are many small areas today where tuberculosis has been eradicated, and with no reason to assume it is inevitable that tuberculosis will appear again in those areas, or if it does, that it cannot be contained and eliminated again and rather rapidly. Why is it unrealistic, then, to assume that we can enlarge the perimeter of each of these lacunae until their borders touch each other and they coalesce into an ever-expanding sea, until finally the last islands of the residual strongholds of tuberculosis have been engulfed, and the last infected person has disappeared?" *James E. Perkins*[1]

While Dr. Perkins' vision has not been fulfilled and perhaps will not be for some time to come, gains have been made in the eradication of tuberculosis; however, in several socio-economic and ethnic groups the disease is still a serious health problem. There has been a continuous decline in tuberculosis mortality rates from the turn of the century to the present, with a sharp decline following the introduction and use of drugs,[2] particularly Isoniazid. Naturally, the next question to arise was whether Isoniazid would be effective in the prevention of tuberculosis as well as in the treatment.

The purpose of this paper is to discuss the chemoprophylaxis of tuberculosis: primary chemoprophylaxis, the use of Isoniazid in exposed but uninfected individuals, and secondary chemoprophylaxis, the treatment with Isoniazid in the tuberculin-positive individual.[3] In addition, attention will be given to the tuberculin-positive individual who falls into the increased-risk category of developing active pulmonary tuberculosis.

Prior to clinical trials, animal studies were carried out to demonstrate whether Isoniazid was effective in the prevention of tuberculosis. Using monkeys, Schmidt[4] showed that Isoniazid therapy could prevent the disease and that this protection lasted for from four to six months following cessation of therapy. Ferebee and Palmer,[5] using guinea pigs, also demonstrated

*Presented as a Medical Grand Rounds at Hennepin County General Hospital, December 5, 1967.

that Isoniazid could prevent active tuberculosis. Protection was inadequate when given at 1 mg. Isoniazid/kg. per day; however, at 5 mg./kg. per day and at 25 mg./kg. per day the animals were completely protected. Following cessation of therapy at ten weeks the animals were protected for a total of 26 weeks. It also appeared that the animals treated with 5 mg./kg. per day developed more immunity than those treated at the higher dosage level. Omoedi Zorini[6] demonstrated the effectiveness of Isoniazid in the prevention of bovine tuberculosis in calves.

Certain individuals have an increased probability of developing tuberculosis. These individuals may be divided into the following categories:[3,7,8]

I. Exposed Tuberculin-Negative Individuals.
II. Positive Tuberculin Test but No Evidence of Clinical Disease.
    A. Recent converter.
    B. Positive skin test in childhood and young adulthood or positive tuberculin test with excess or continued exposure.
    C. Strong tuberculin reaction.
    D. Positive tuberculin reactors in mental institutions.
    E. Positive skin test associated with other conditions such as steroid therapy, uncontrolled diabetes, silicosis, sarcoidosis, lymphomas and leukemia, pregnancy, malnutrition (including alcoholism), post-gastrectomy, and measles or whooping cough.
III. Positive Tuberculin Test with Roentgenograph Findings.
    A. No drug therapy.
    B. Inadequate drug therapy.
    C. Far advanced disease.
    D. Changing roentgenographic pattern.

Results of Clinical Trials

In all the trials to be discussed, unless otherwise stated, a positive tuberculin test was a reaction greater than 5 mm. induration using intermediate strength Purified Protein Derivative Test. When placed on Isoniazid the individual was given therapy at an average dosage of 5 mg./kg. per day up to 300 mg. daily.

Exposed Tuberculin-Negative Patient

All persons exposed to a patient with active tuberculosis must be given prophylactic Isoniazid while exposure exists. Management of the tuberculin-negative patient recently exposed to tuberculosis may be handled in different ways.

In a double blind study on tuberculin-negative patients, Egsmose et al.[9] showed a 7% decrease in the tuberculin conversion in those patients on prophylactic Isoniazid therapy compared with the control group. The patients had received Isoniazid 5-10 mg./kg. per day for a period of one year and had been observed for two to four years. He also noted a significant decrease in the rate of development of active pulmonary tuberculosis in those patients on prophylactic Isoniazid therapy (Table 1).

Ferebee and Mount[10] found that Isoniazid was effective in the exposed tuberculin-negative individual. Five cases of primary tuberculosis developed in the Isoniazid group and 16 in the placebo group during the treatment year. Some of the patients on Isoniazid may have been infected at the time therapy was initiated.

Dormer et al.[11] used Isoniazid in infants of mothers who had active tuberculosis and were in various stages of therapy. The mothers and infants were kept in an open ward, and most infants were breast fed. The infants were given 25 mg. of Isoniazid syrup twice daily, increased to 50 mg. twice a day at six months of age. There were no cases of tuberculosis found in the infants during the observation period.

These studies would indicate that Isoniazid is of benefit in the exposed tuberculin-negative patient. An alternate route would be to observe these patients closely with repeated skin tests and treat them upon conversion of the skin test.[12] However, if the family is large with both positive and negative reactors, it would be simpler and probably more effective to treat the entire family with Isoniazid.

The person who has had an extremely large exposure to tuberculosis, such as may occur in a laboratory accident or in resuscitation of a tuberculous patient, should be placed on prophylaxis, with skin tests repeated every three months.

Positive Tuberculin Test but No Evidence of Clinical Disease

A. Recent Converter

The recent tuberculin converter falls into the high-risk area of developing pulmonary tuberculosis. However, the exact time of conversion is frequently unknown, making it difficult to establish or interpret statistics.

Chiba et al.,[13] in a controlled double blind study composed of recent tuberculin converters, gives us some idea as to the prognosis of this group as well as the effect of prophylaxis. Two hundred seventy-four patients in his group were treated with either Isoniazid or a Isoniazid-Paraaminosalicylate combination, while 274 were on placebo alone for the same one-year period. In a period of observation ranging from six to twelve years, nine of the treated group and 23 of the control group developed pulmonary tuberculosis. This work led to a large-scale study by the same authors in which over 4,000 patients were treated and then observed for a one- to five-year period. In terms of person years, 0.24% of the treated group and 1.25% of the control

TABLE I

Significance of Difference in Incidence Rates Observed in Control and Isoniazid Groups

Initial Status	During first year of study	Control Group		Isoniazid Group		Significance of the difference at the 5% probability level
		Incidence rate (%)	SE	Incidence rate (%)	SE	
Tuberculin non-reactors	Tuberculin conversion	13.19	3.13	5.68	2.07	Significant
	Development of pulmonary lesions	4.32	1.95	1.86	1.09	Not significant
	Excretion of tubercle bacilli	3.78	1.53	0.00	0.00	Significant
Tuberculin reactors	Excretion of tubercle bacilli	1.60	0.87	1.04	0.72	Not significant
Pulmonary lesions (active & inactive)	Excretion of tubercle bacilli	21.43	8.08	0.00	0.00	Significant

Egsmose et al.[9]

group developed pulmonary tuberculosis.

In another series by Groth-Petersen et al.[14] of patients with positive tuberculin and negative chest x-rays, the risk of developing pulmonary tuberculosis was 27 per 100,000.

Ferebee and Mount,[10] in a study involving 25,512 household members of an index case, found 479 with active tuberculosis or 19 per 1,000. It is not known how long these may have been active, but probably many were recent converters. Of those individuals who had a positive skin test and negative chest x-rays, 16 in the placebo group and four in the Isoniazid group developed extra-pulmonary tuberculosis. Also 62 patients developed pulmonary tuberculosis in the placebo group compared with 14 in the therapy group. The risk was well correlated with the skin test, ranging from 8.3 per 1,000 for those with 5-9 mm. positive reaction to 20 per 1,000 for those of 20 mm. or more induration.

Meyers et al.[15] followed a group of 149 children who were known recent converters, with a mean age of 14.6 years at time of conversion. Eleven (8.5%) had developed tuberculosis with a mean duration from skin test conversion to active tuberculosis of four years with a range of a few months to about 25 years.

In another publication Meyers et al.[16] reported 195 children, ages six to 12, who were known converters. Eleven (7.4%) have developed clinical disease with four deaths. Onset of clinical disease following conversion ranged from three months to seven years. One patient was found to have advanced disease 24 years after conversion; however, as she had not been followed, the time of onset of clinical disease was not known.

In another review[17] the rate of clinical disease in the tuberculin-positive patient is estimated to be 5% over an indefinite period of time.

Steinfield and Cohen[18] have advocated Isoniazid therapy at 10 mg./kg. per day for two years' duration. They have treated all contacts in the household regardless of skin test, and in 442 patients who have been followed for over three years none have developed clinical tuberculosis.

B. Positive skin test in childhood and young adulthood or positive tuberculin test with excess or continued exposure.

Meyers et al.[19] followed a group of 750 children with positive skin tests who were ages one to six at the time the study was instituted. Most of them were followed for several years. Of the group that had positive skin tests with tuberculous primary infiltrates, seven of 151 patients died from tuberculosis. An additional seven developed clinical disease and were treated with satisfactory long-term survival. Meyers also reported on 599 children who had a positive tuberculin test but normal chest x-rays. Of this group 41 developed clinical tuberculosis with 15 deaths.

In another of Meyer's studies[16] involving the six-to-12 age group, of 1,247 tuberculin-positive children who were followed, 25 deaths (2%) occurred.

Mount and Ferebee[20] reported a double blind study of children with primary tuberculosis and found that the risk of developing complications was significantly higher in those under six years of age. They also found Isoniazid to be very effective, especially in extrapulmonary complications. Of those children on Isoniazid, 30 developed pulmonary complications compared with 46 taking the placebo. Extrapulmonary complications occurred in 31 cases on placebo compared with only two cases in the Isoniazid-treated group.

During a follow-up period of two years, eight patients who had been on the placebo developed complications compared with four who had been taking Isoniazid. This would indicate that Isoniazid had some prolonged beneficial effect in addition to the observations while on therapy.

One can only concur with Mitchell[8] that all patients under five years of age with a positive skin test should be treated.

It has often been thought that children in the six-to-12-age group had an increased resistance to tuberculosis. While this may be true, 2% of Meyers' series[16] died of their disease.

It has been felt that since there is an increased susceptibility to tuberculosis during puberty and adolescence, prophylaxis during this period should be recommended.[7] Steinfeld[18] suggests treating all tuberculin-positive individuals 20 years of age or younger. Meyers' studies,[15] however, did not show an increased susceptibility in this age group. He felt that mortality and morbidity studies reflected natural progression of the disease in a person infected at a younger age.

In a group of tuberculin-positive young adults in a university in Poland a double blind study showed the effectiveness of Isoniazid prophylaxis. Of the placebo group 2.2% developed tuberculosis, while none in the therapy group did.[21]

Not infrequently an adult patient is discovered who has a positive skin test along with a negative x-ray, but there have been no double blind studies in this group of patients.

All contacts of an active case of tuberculosis are considered high risk and should receive chemoprophylaxis. Gregg and Kuemmerer[22] in 1961 investigated the contacts of 102 index cases of tuberculosis and found 29 active cases on first examination, with an additional 21 cases on subsequent testing. Prophylactic chemotherapy was given to all contacts with a 56% decrease in the incidence of active tuberculosis among household contacts.

Omoedi Zorini[6] reported that 2.14% of his household contacts which served as controls developed tuberculosis, compared with 0.13% of those treated with Isoniazid.

Egsmose et al.,[9] in a study of household contacts, noted a 1.6% activation rate among the controls as compared with 1% in those on Isoniazid therapy; but he did not consider this a significant decrease.

Comstock,[23] in a double blind study from Alaska, reported an incidence rate of active tuberculosis of 1.36% per year in the control group compared with 0.43% in the Isoniazid group, and stated that Isoniazid showed a 64% reduction in the number of expected cases.

Ferebee and Mount,[10] in examining over 25,000 contacts of index cases, found 479 patients with active tuberculosis or 19 per 1,000. All contacts were then placed on chemoprophylaxis for one year. Pulmonary tuberculosis developed in adults in 62 cases on placebo and in 14 patients on Isoniazid therapy.

In a follow-up study from Alaska, Comstock et al.[24] reported an incidence rate of 4.67% in the placebo group compared with 1.9% in the Isoniazid-treated group. The risk of tuberculosis developing during the study period was greatest among positive tuberculin reactors and young adults.

Horwitz et al.[25] reported a double blind study involving 8,081 adults from Greenland, all of whom were assigned to either the placebo or the Isoniazid therapy group regardless of their tuberculin status. Their studies showed an incidence rate for the first year in the control group of 19 per 1,000 com-

pared with 13 per 1,000 in the Isoniazid group. During a six-year follow-up, the Isoniazid group continued to show a beneficial effect, with a decreased incidence rate compared with the placebo group (Table 2).

TABLE 2
Incidence of Respiratory Tuberculosis by Year in Follow-Up Period

Year in follow-up period	Placebo		Isoniazid	
	No.	Annual No. per 1,000	No.	Annual No. per 1,000
1st	73	19	53	13
2nd	68	17	42	10
3rd	55	14	40	10
4th	45	12	45	11
5th	52	13	33	8
6th	30	8	25	6
TOTAL	323	14	238	10

Horwitz et al.[25]

A study was conducted by Mount and Ferebee[26] of household contacts of previously active cases, where the exposure had occurred from a few months to several years prior to starting the study. Examination of these contacts revealed ten with active tuberculosis or a rate of 3.5 per 1,000, again indicating the importance of follow-up. Among the placebo group nine developed active tuberculosis or a rate of 6.7 per 1,000, while three in the Isoniazid group developed clinical tuberculosis. Eight of the nine patients in the placebo group had had positive tuberculin tests at the initiation of the study.

C. Strong Tuberculin Reaction.

As mentioned previously, Ferebee and Mount[10] observed a correlation between the extent of the tuberculin reaction and the risk of developing tuberculosis.

The group from Denmark[14] also found that the size of the reaction was important in relation to the risk of developing tuberculosis, particularly in the younger age groups. For the age range 15-24 years, 6-11 mm. induration was associated with an incidence of 24 per 100,000, while with a reaction from 18-23 mm. they found an incidence of 87 for 100,000.

Comstock et al.[24] did not concur. They noted that the greatest risk occurred in those who were originally negative, with little difference in incidence among the positive reactors. Others[8,21] advocate therapy of the strong reactor.

D. Positive Tuberculin Reactors in Mental Institutions.

Ferebee et al.[27] did a study concerning the effectiveness of Isoniazid in preventing active tuberculosis in several U.S. mental institutions, involving over 25,000 patients. During the medication year which includes the three months following cessation of therapy, 21 in the placebo group developed active tuberculosis compared with four who had received Isoniazid. Three of those four had abnormal x-rays at the beginning of the study but responded well to Isoniazid therapy. The reason for becoming active while on the drug is unknown. Isoniazid prevented three fourths of the cases that would have developed had the drug not been given.

E. Positive Skin Test Associated with Other Conditions Such as Steroid Therapy, Uncontrolled Diabetes, Silicosis, Sarcoidosis, Lymphomas and Leukemia, Pregnancy, Malnutrition (Including Alcoholism), Post-gastrectomy, and Measles or Whooping Cough.

Development of tuberculosis in the patient with silicosis is a frequent and severe complication. Monaco[28] reported that 98% of patients with silicosis had a positive tuberculin reaction and that 63% would die of tuberculosis. In a controlled study he treated patients with Isoniazid 10 mg./kg. per day or placebo for three months, alternating with three months of rest for a period of two years. He found that 0.75% of the treated group developed active tuberculosis compared to 10.21%.

Omoedi Zorini[6] reported a study involving 788 cases of silicosis with either positive tuberculin or exposure to tuberculosis, who were treated for a period of two years. Of 370 controls, 7% developed tuberculosis compared with 1.14% of the therapy group.

There is increased risk of tuberculosis in the patient who has had gastric surgery. Chofnas and Love[29] reported on 250 patients, of whom 17 (6.8%) had had surgery, thirteen of them gastric surgery prior to the onset of pulmonary tuberculosis.

Waingortin and Lorge[30] presented a series of 27 cases of tuberculosis associated with gastrointestinal disease, twelve of them after surgery for peptic ulcer. Four patients developed symptoms after thoracoplasty. In seven pulmonary tuberculosis preceded the onset of peptic ulcers. An additional four had ulcer symptoms preceding the onset of tuberculosis; however, these patients had had only medical therapy. The authors noted that physical and emotional stress were very prominent in this group of individuals.

Borner[31] observed an increased incidence of tuberculosis in his series of post-gastrectomy patients and also noted a much higher death rate in these patients. While various factors such as starvation, malabsorption, metabolic abnormalities, stress and poor hygiene have been postulated as etiologic factors, no true cause for this increased incidence of tuberculosis has been found. While Borner did not find any definite studies showing the benefit of prophylaxis in this group, certainly they should be observed closely with repeated chest x-rays and possibly be considered for prophylactic therapy.

Management of the pregnant tuberculosis patient presents a unique problem; studies in the past have been somewhat contradictory regarding the effect of pregnancy upon tuberculosis. In previous years it was thought that tuberculosis had an adverse effect on pregnancy; at times abortion was even recommended and performed.[32]

Rosenbach and Gangemi[33] presented their results in a series of 150 patients with active tuberculosis who were observed during 241 pregnancies. While 23 patients showed progression of tuberculosis, most of these refused to follow medical advice. Nineteen showed regression during pregnancy and the postpartum period. The authors concluded that pregnancy had little effect on the progression of tuberculosis.

Pridie and Stradling[34] reported on 103 pregnancies in 72 patients with pulmonary tuberculosis, twenty of whom relapsed some time during the pregnancy or in the succeeding year. No relapses occurred in the group given chemotherapy during pregnancy, about half of these having received no chemotherapy previous to the pregnancy. All the relapses occurred in the group not given chemotherapy during pregnancy, 17 of whom had never

had chemotherapy for the disease. Pridie et al. therefore concluded that relapse could be effectively prevented during pregnancy by chemoprophylaxis (Table 3).

TABLE 3
Relapse and Chemotherapy

	Chemotherapy During Pregnancy			No Chemotherapy During Pregnancy		
	Initial Chem.	No Initial Chem.	Total	Initial Chem.	No Initial Chem.	Total
Relapse	0	0	0	3	17	20
No relapse	22	6	28	21	34	55
Total	22	6	28	24	51	75

Pridie and Stradling[34]

Rovinsky and Guttmacher[32] suggest the following when dealing with pregnancy in tuberculosis: If the patient has a healed Ghon complex on x-ray and a positive skin test but no other evidence of the disease they would withhold all therapy and observe only. If the patient has had pulmonary tuberculosis but is now judged inactive they recommend prophylaxis beginning with the seventh month of pregnancy. A recent skin converter should be given Isoniazid therapy. They also suggest that a strongly positive tuberculin reactor be given prophylaxis.

Grzybowski[12] recommends chemoprophylaxis in tuberculin-positive children who develop measles and whooping cough.

While statistics are lacking it is well known clinically that prolonged steroid therapy may reactivate quiescent tuberculosis. Animal studies and clinical reports are discussed in a review by Johnson and Davey.[35] Many studies showed that steroids have an adverse effect on the tuberculous animal; however, others found no difference. Case reports indicated that while an occasional patient improved, the majority became worse while on steroids. Others[36,37] reported patients with various diseases including rheumatoid arthritis, sarcoiditis, lupus erythematosus and polyarteritis who developed tuberculosis while on steroids. All patients with a positive skin test or inactive tuberculosis should receive prophylaxis while on steroids. The patient with sarcoidosis should also receive Isoniazid therapy whenever long-term steroids are given.

Nutrition is an important factor in many diseases, including tuberculosis. Keys et al.[38] studied the state of nutrition in several countries during World Wars I and II. While many other factors, including rest, sanitation, overcrowding, poor medical care for the sick, and better housing are significant, changes in the incidence of tuberculosis can be closely correlated with the diet. Quality as well as quantity were considered important factors.

Patients with lymphoma, especially Hodgkin's disease, and leukemia have an increased incidence of tuberculosis. Parker et al.[39] reported that 30% of patients with Hodgkin's disease also had tuberculosis. Arden and Rottino,[40] in a series of 162 autopsies on patients with Hodgkin's disease, found that five had died (3%) of miliary tuberculosis. In two of these, Hodgkin's disease had been completely arrested. The marked difference in incidence in these series may reflect the overall decrease in the incidence of tuberculosis. Arden et al.[40] felt that steroids or irradiation therapy had no effect on the development of tuberculosis. Haynes and Begg[41] reported two patients with lymphoma who died of miliary tuberculosis following therapy with steroids and/or

chemotherapeutic agents. Morrow and Anderson[42] reported leukemia or lymphoma in a series of patients exposed to the atomic bomb in 1945. Of patients with chronic myelogenous leukemia 23% had tuberculosis. While there were only twelve patients with myelofibrosis, four of these had miliary tuberculosis. There was no increase in tuberculosis in the acute leukemias.

It has long been known that diabetes and tuberculosis are frequently associated, for reasons still not evident. Halden and Hiltz[43] reported 11% of their tuberculosis patients to have diabetes and also noted that the diabetes was more severe in those patients with far advanced tuberculosis. Of 13 patients who reactivated, eleven were discovered to have diabetes at the time of reactivation. In a series of young men with tuberculosis, Nichols[44] found that 22% had diabetes or abnormalities in glucose tests.

Positive Tuberculin Test with Roentgenographic Findings

There are large numbers of individuals who have had clinical tuberculosis and who have abnormal x-rays. Of this group it is estimated that 10,000 will relapse annually.[45] Depending upon adequacy of treatment, state of disease, etc., some of these have a much higher risk of developing active tuberculosis, being a hazard to themselves as well as to others in their environment. The balance of this paper will be concerned with identifying those of greatest risk so that close observation and appropriate therapy may be given.

Phillips[46] reported a series of 312 tuberculous patients who were followed for three years after discharge from the hospital, only two thirds of whom had received some form of chemotherapy. During the three-year period he noted that 80 patients (25.6%) had clinical relapses. This was well correlated with the extent of clinical disease, with 14% occurring in the minimal category, 24% in the moderately advanced group, and 32% in those with far advanced tuberculosis.

In a series of 112 patients Phillips[45] followed for 15 years he found that relapse had occurred in 47 patients, 17 of whom had had more than one reactivation. Eighty per cent had never received chemotherapy, and the remaining twenty per cent had received inadequate chemotherapy.

The effectiveness of adequate chemotherapy in preventing relapse is demonstrated in a series of 109 patients followed for six years after hospital discharge[47] (Tables 4 and 5).

TABLE 4

Effect of Chemotherapy Regimen

Regimen Employed	No. of Patients	No. of Relapses	Relapse Incidence
Isoniazid combinations	72	15	7%
Streptomycin combinations	15	2	13%
Mixed combinations	7	1	14%

TABLE 5

Duration of Chemotherapy

Total Period Chemotherapy Employed	No. of Patients	No. of Relapses	Relapse Incidence
Less than 18 months	14	3	21%
Less than 2 years	38	6	16%
Two years or more	56	2	4%
Three years or more	17	0	0%

Phillips, S.[47]

Best results were obtained with the use of Isoniazid combinations in which an incidence of 7% occurred. Combinations of other drugs were associated with a 14% relapse rate. Duration of therapy was important, with a 21% relapse in those treated less than 18 months compared with 4% in those treated two years or more.

Comstock[48] presented a series of 1,008 cases of inactive but untreated tuberculosis which he followed for up to ten years. Sixty-eight patients (6.7%) developed active clinical disease, most of which occurred during the early part of the observation period. The risk was much greater for Negroes compared with Whites; it was also significantly higher in the advanced disease group. For example, the incidence in Negroes with advanced disease was greater than 30%. In the younger age group those with minimal and suspected disease were also high risk.

Fuchs[49] reported on 3,214 patients, some of whom had been followed in excess of 20 years. In those with adequate drug treatment there was a 2% risk of reactivation over a five-year period. The risk of reactivation was three and one-half times greater in those with no or inadequate chemotherapy, while the patient who was uncooperative and inadequately treated showed a 37.5% risk of reactivation of the disease. The patient with a changing x-ray pattern also is a high risk.

Katz et al.[50] used prophylactic Isoniazid in a group of 247 patients with inactive tuberculosis. They received 300 mg. per day for two years and were observed for a period of four years following cessation of therapy. During the treatment period Katz found that Isoniazid had a significant effect in preventing reactivation with an additional protective effect which lasted about two years after cessation of therapy.

Chiba et al.[13] also used prophylactic Isoniazid in a group with inactive pulmonary tuberculosis. The control group showed a relapse of 4.5% compared with a 0.72% relapse rate in the treated group, demonstrating the beneficial effect of prophylaxis.

Ferebee et al.[27] found an activation rate of 13 per 1,000 in a control group compared with 2.5 per 1,000 in a treated group.

Isoniazid in Prophylaxis

Ferebee[10] notes that Isoniazid is an ideal drug for the chemoprophylaxis of tuberculosis. It is extremely effective, safe, inexpensive, and well tolerated. Side reactions to Isoniazid can be divided into two categories: hypersensitivity and toxicity.[51] The most frequent reactions involve the nervous system as well as the gastrointestinal tract. Various reactions including fever, skin reactions, hepatitis, convulsions, ataxia, optic atrophy, toxic encephalopathy along with agranulocytosis have been reported, but fortunately are extremely rare. In the clinical studies[9,10,18,23,25,26,27] all studies reported less than 2% side reactions, and most studies reported less than a 1% incidence. Certainly the patient should be observed for evidence of pyridoxine deficiency and treated for it if present. Elderly or malnourished patients should receive this drug routinely.

Kapur et al.[52] reported that one patient developed resistant tubercle bacilli following Isoniazid prophylaxis. Many observers were concerned about this possibility. While sensitivity studies were rarely carried out, drug resistance was not found to be a clinical problem.[23,24,25,27]

Summary

Isoniazid is found to be a very effective agent in the chemoprophylaxis of tuberculosis. It is recommended that those individuals who have an increased risk of tuberculosis be placed on at least one year of Isoniazid prophylaxis. Active tuberculosis must be excluded by appropriate means prior to instituting prophylactic Isoniazid therapy.

References may be secured from the Grand Rounds Editor.

What's New?

Abbott Laboratories— Nuclear medical instruments for small hospitals, clinics and physicians' offices.

Three new instruments designed to make radioisotopes testing available in smaller hospitals and clinics have been announced by Abbott Laboratories. These instruments will permit tests of thyroid function, red blood cell mass, plasma volume and latent iron-binding capacity by small, self-contained units. The three models include two well counters and one scaler analyzer. Each unit measures 12-1/2 by 13 inches by 4-1/16 inches high and weighs from 25 to 35 pounds. Costs range from $2300 to $2700. Further information on the LOGIC series counting systems is available from Abbott Laboratories, North Chicago, Illinois, 60064.

Wyeth Laboratories— A new oral contraceptive named "OVRAL" has been introduced in the United States by Wyeth Laboratories. This pill combines an estrogen with a progestogen, norgestrel. Norgestrel is a synthetically prepared steroid. This new oral contraceptive is presented in an attractive plastic dispenser with a printed "memory" listing the days of the week to assist the patient with proper dosage.

Winthrop Laboratories—Small intravenous doses of a new non-narcotic analgesic were found effective in reducing postoperative pain, in lowering the overall need for analgesia and in shortening the duration of hospitalization. The analgesic, Talwin, brought satisfactory pain relief rapidly and safely in 86.9 percent of the patients given injections.

Glenbrook Laboratories—Aspirin is well known for pain relief in the treatment of arthritis. Recent experiments, however, have shown that the salicylates are also anti-inflammatory, aiding joint movements and grip strength in cases of rheumatoid arthritis.

Derivatively Speaking

Sacrum—from Latin *sacer* (sacred).



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Contraindications: Dextro-amphetamine sulfate: In hyperexcitability and in agitated prepsychotic states. Previous allergic or idiosyncratic reactions to meprobamate.
Precautions: Use with caution in patients hypersensitive to sympathomimetic compounds, who have coronary or cardiovascular disease, or are severely hypertensive.

Dextro-amphetamine sulfate: Excessive use by unstable individuals may result in psychological dependence.

Meprobamate: Careful supervision of dose and amounts prescribed is advised, especially for patients with known propensity for taking excessive quantities of drugs. Excessive and prolonged use in susceptible persons, e.g. alcoholics, former addicts, and other severe psychoneurotics, has been reported to result in dependence on the drug. Where excessive dosage has continued for weeks or months, reduce dosage gradually. Sudden withdrawal may precipitate recurrence of preexisting symptoms such as anxiety, anorexia, or insomnia; or withdrawal reactions such as vomiting, ataxia, tremors, muscle twitching and, rarely, epileptiform seizures. Should meprobamate cause drowsiness or visual disturbances, reduce dosage and avoid operation of motor vehicles, machinery or other activity requiring alertness. Effects of excessive alcohol consumption may be increased by meprobamate. Appropriate caution is recommended with patients prone to excessive drinking. In patients prone to both petit and grand mal epilepsy meprobamate may precipitate grand mal attacks. Prescribe cautiously and in small quantities to patients with suicidal tendencies.
Side Effects: Overstimulation of the central nervous system, jitteriness and insomnia or drowsiness. Dextro-amphetamine sulfate: Insomnia, excitability, and increased motor activity are common and ordinarily mild side effects. Confusion, anxiety, aggressiveness, increased libido, and hallucinations have also been observed, especially in mentally ill patients. Rebound fatigue and depression may follow central stimulation. Other effects may include dry mouth, anorexia, nausea, vomiting, diarrhea, and increased cardiovascular reactivity.

Meprobamate: Drowsiness may occur and can be associated with ataxia; the symptom can usually be controlled by decreasing the dose, or by concomitant administration of central stimulants. Allergic or idiosyncratic reactions: maculopapular rash, acute nonthrombocytopenic purpura with petechiae, ecchymoses, peripheral edema and fever, transient leukopenia. A case of fatal bullous dermatitis, following administration of meprobamate and prednisolone, has been reported. Hypersensitivity has produced fever, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, stomatitis, proctitis (1 case), anaphylaxis, agranulocytosis and thrombocytopenic purpura, and a fatal instance of aplastic anemia, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity, usually after excessive dosage. Impairment of visual accommodation. Massive overdosage may produce drowsiness, lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse.

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The Health of the Nation

A special summer lecture series sponsored by the University of Minnesota Hospitals and local member hospitals of the Council of Teaching Hospitals, American Association of Medical Colleges (i.e., Miller, Ramsey County, Hennepin County, Veterans, Mt. Sinai) will be held at the University of Minnesota Health Sciences Center during the summer months. The objective of the meeting is to bring together community leaders and health professionals to focus on major health issues of the day.

This will be an invitational conference with participants including representatives of medical staffs, boards of trustees and hospital administration from the metropolitan area. In addition, representatives will be in attendance from various local and state health organizations as well as members of the faculties of the health science units. The meetings, which will be held in Mayo Auditorium at 12:00 noon. Any individuals who do not receive an invitation and would like to attend some of these sessions should contact C. Thomas Smith, Jr. at Box 605, University of Minnesota Hospitals.

Friday Noon Summer Series
Mayo Auditorium
University of Minnesota Health Science Center

	Speaker	*Title or Topic Area*
July 5	Dr. Raymond D. Pruitt Director Mayo Graduate School of Medicine	The Teaching Hospital
12	Dr. Richard M. Magraw Assistant Director for Extramural Relations Bureau of Health Services Relations, U.S.P.H.S. Silver Spring, Maryland	Medicine and Society: Professional Roles in Retrospect and Prospect
19	Mr. Walter J. McNerney President Blue Cross Association Chicago, Illinois	The Organization and Financing of Health Services
26	Dr. Robert L. Berg Professor and Chairman Department of Preventive Medicine University of Rochester Medical Center Rochester, New York	Priorities in Health Care
August 2	Mrs. Ann R. Somers Research Associate Princeton University Princeton, New Jersey	Community Areawide Health Planning
9	Mrs. Rosemary Stevens Research Associate Brookings Institute Washington, D. C.	Medical Specialization and Public Policy
23	Dr. Vernon Wilson Executive Director of Health Affairs University of Missouri Columbia, Missouri	Future Patterns in the Provision of Health Care
30	Mr. John Barr, Dean Graduate School of Business Northwestern University Chicago, Illinois	Report of the Secretary's Advisory Committee on Hospital Effectiveness
September 6	Dr. James G. Haughton First Deputy Administrator Health Services Administration New York, New York	Can the Poor Use the Present Health Care System?
13	John G. Freyman, M.D. General Director Boston Hospital for Women Boston, Massachusetts	The Role of the Affiliated Community Hospital in a University Teaching Program

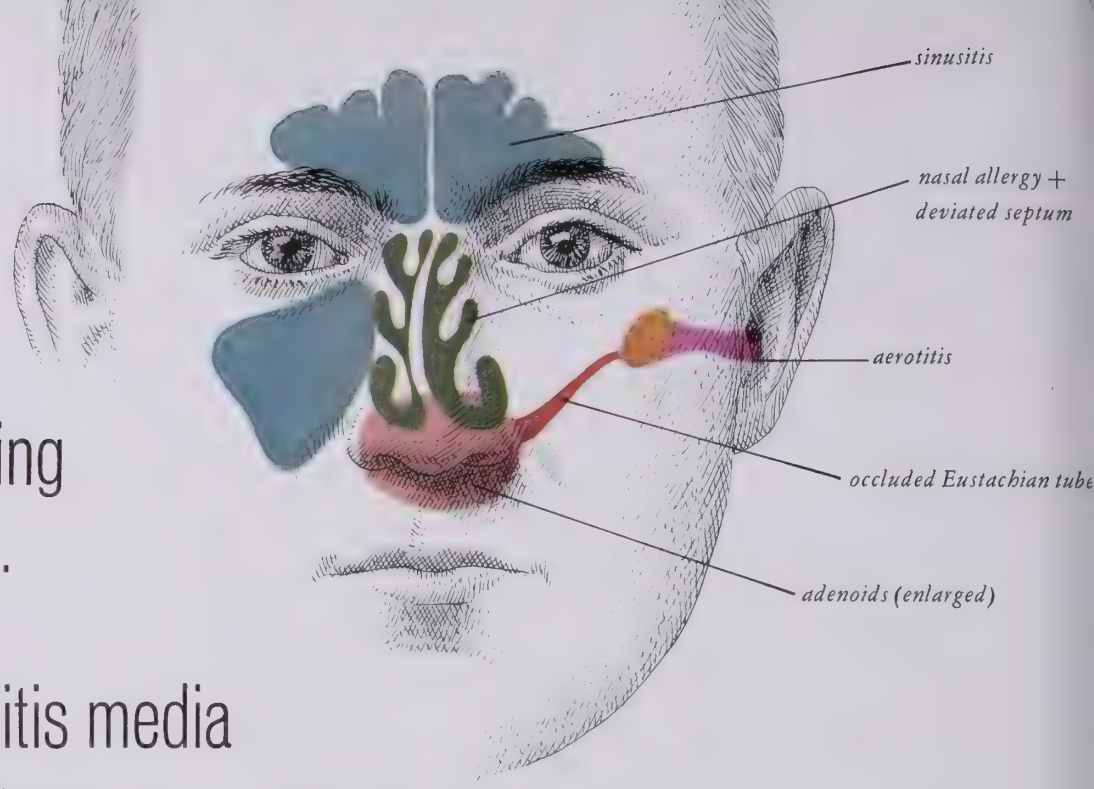
vol. 3, no. 2

DORSEY Season

A journal within a journal published periodically in the interests of better medicine by Dorsey Laboratories, a division of The Wander Company, Lincoln, Nebraska 68501. Address communications to Keith W. Sehnert, M.D., Medical Director.



this issue:
serous otitis media
an original article
by Robert H. Lofgren, M.D.



the complaining earache... key to serous otitis media

Robert H. Lofgren, M.D.
Associate Surgeon, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts

Serous otitis media is probably the most common ear problem in children, especially in the wintertime. Diagnosis is usually easy in adults, but may be quite difficult in children, especially the very young child where one has to depend almost entirely on the physical findings.

The symptoms of serous otitis are a fullness in the ear, a mild hearing loss and mild earache. The earache can best be described as a "complaining earache" instead of a "screaming earache" as found in purulent otitis media. A young child may be irritable and pull at the ear. In milder cases, and as the ear recovers, gurgling and popping noises can be heard in the ear.

On examination one may see a yellow tympanic membrane and if a fluid level is present the diagnosis becomes easy. However, the eardrum may be dull gray, or slightly pink, or even perfectly normal. Pneumomassage using a Siegle otoscope or a closed-head electric otoscope must be done on both ears, otherwise the diagnosis will be frequently missed. Attempted movement of the drum with the pneumatic otoscope produces either a sluggish motion of the drum or no motion at all instead of the easily movable normal drum. The Rinne test is negative and there is a 15-20 decibel conductive hearing loss. The bone conduction may be better than normal and an air-bone gap may exist even with the air conduction within normal limits. Occasionally one finds a false nerve deafness on the audiogram when thick glue-like fluid causes immobility of both the oval and round window. Both conditions return to normal when the fluid is removed, but they make the interpretation of screening audiograms very difficult.

There is no single cause for serous otitis. One factor always present is blockage of the eustachian tube, but this alone is not enough to produce fluid. There must also be an inflammatory reaction. Blockage of the eustachian tube may be caused by many conditions. In children the most common cause is enlarged adenoids. In the summer the next most common cause is allergy. Upper respiratory infections or influenza are common causes in the winter. Nasal allergy, acute and chronic sinusitis, nasal septal deformity and cleft palate can all cause eustachian tube obstruction. Some children may have a congenitally small eustachian tube, but fortunately they usually "grow out of the problem."

The first sign of a nasopharyngeal tumor is often a serous otitis. One must always rule this out in any adult who later in life develops repeated or persisting serous otitis. Causes sometimes overlooked are nasogastric tubes after surgery, simple obesity and cardiorenal disease, which may produce congestion in the mucosal lining of the eustachian tube. In recent years we have been seeing a new cause—acute otitis media, where the patient is adequately treated with antibiotics but where drainage has not been

established either through the eardrum or down the eustachian tube. A sterile exudate is left in the middle ear.

The inflammatory response may be caused by a marked negative pressure as in air otitis from flying, or it may be from a mild bacterial or viral infection in the middle ear. Serous fluid is a good culture medium and will frequently go on to purulent otitis media, especially if the original blockage was caused by an infectious process such as acute rhinitis or adenoiditis. When the infection heals there may be scarring in the middle ear mucosa. Mucous glands develop in this tissue and pour out a thick mucoid material. This ear usually looks normal until a pneumatic otoscope is used. The objectives in treating serous otitis are to remove the obstructing agent and to provide drainage from the middle ear. Often this can be accomplished by decongestants and nose drops. If large obstructing adenoids are present they should be removed. Sinusitis should be treated with oral decongestants or nose drops, plus antibiotics where indicated. Nasopharyngeal tumors should be treated. Allergies should be treated with antihistamines and, where indicated, by desensitization.

If the fluid does not clear with medical treatment within a week or two, a myringotomy should be done. If there is a question of active infection or if the fluid looks purulent, as is seen at the conclusion of acute otitis, cultures are taken. On adults this can be done in the office without anesthesia. It is no more painful than an intravenous needle for a blood test. A good safe topical anesthetic has a tremendous psychological value to the patient. Children under the age of 1 require no anesthesia. Between the ages of 1 and 3 anesthesia is not absolutely essential although a general anesthetic may be used to avoid the child's possible mistrust at follow-up examinations. I usually do the myringotomy at the same time as the adenoidectomy if the adenoids are enlarged. Once drainage has been established with decongestants or by myringotomy, positive pressure inflation of the middle ear is invaluable in forcing out the serous fluid and keeping it from reforming. The patient can do this himself by performing the Valsalva maneuver. This should be done several times a day, by taking a deep breath, holding the nose and blowing hard against the closed lips for a second or two.

In resistant cases where the fluid reforms as soon as the myringotomy heals, small polyethylene tubes are inserted through the myringotomy site. Insertion of the tubes, even in adults, usually requires an anesthetic. Good anesthesia can be obtained by infiltrating the canal wall with a local anesthetic, using a #27 needle. Once inserted the patient has no sensation of the tubes' presence. Be careful to caution the patient or parents not to allow any water to get into the ear canal while a myringotomy is open or a tube is in place. Water can be kept out by a pledget of lamb's wool in the ear canal or a cotton pledget thickly coated on the outside with petroleum jelly. I check these patients a week after a myringotomy to be sure it is healed and at two month intervals until the tubes have fallen out, usually within three to six months after insertion.

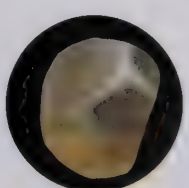
The mucoid type of fluid is so thick and tenacious that it is appropriately called a glue ear. It is aspirated only with difficulty through the eardrum, and occasionally must be removed through a tympanotomy. This thick, glue-like fluid is prone to recur, as the myringotomy usually heals long before the mucous membrane has returned to normal. Repeated myringotomies, as many as ten or twenty, were formerly required for this condition. Now polyethylene tubes are inserted initially when this thick, glue-like material is found. At times a subacute mastoiditis may accompany the serous otitis, which will necessitate a simple mastoidectomy before the condition can be eradicated. Usually the thin serous fluid readily responds to decongestants or to a myringotomy and removal of the eustachian tube obstruction. Occasionally, however, even serous fluid will repeatedly reform. For this, resection of the tympanic plexus of nerves which lies on the promontory of the middle ear has been carried out, as the tympanic branch of the glossopharyngeal nerve is the secretomotor nerve to the ear.

Failure to diagnose serous otitis is the most common cause of the recurrent, almost continuous otitis me-

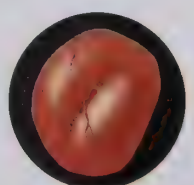
Otoscopic Views



Normal



Acute Serous



Acute Purulent



Chronic Serous

dia seen in young children. In these cases a myringotomy will frequently provide a long-term cure without adenoidectomy or any other surgery. Failure to do this may allow the condition to go on to acute or subacute mastoiditis. Adhesive otitis media with scar tissue binding down the ossicles or tympanosclerosis may also result with permanent impairment of hearing. The prognosis for hearing with adhesive otitis or tympanosclerosis is usually poor. If the adhesions are removed, they reform, and the same is frequently true of tympanosclerosis even after a tympanoplasty. For many of these people a hearing aid is the only solution. The constant negative pressure in long standing serous otitis media may draw in either Schrapnell's membrane or the posterior superior portion of the eardrum forming a pocket to cause a chronic otitis media with cholesteatoma, which may not become apparent until twenty or thirty years later.

The non-medical complications of improper diagnosis or treatment may be even more serious. The irritable child, the frequent bouts of acute purulent otitis media with pain and fever, the expense of antibiotics and doctors, and the time lost from school or work affect the entire family.

In summary, serous otitis has many causes. There is a blocking of the eustachian tube and an inflammatory reaction in the middle ear mucosa, the latter usually caused by a mild infection. The treatment is to provide immediate drainage by decongestants and where necessary, by a myringotomy. The obstructing agent must be removed by surgery if it is adenoid or by oral decongestants, and antihistamines or nasal spray if it is an upper respiratory infection or allergy. Occasionally resistant cases require plastic tubes placed through the eardrum or other more radical surgery. Failure to treat properly leads to hearing loss which may be permanent, repeated acute otitis media or possibly even chronic otitis media with cholesteatoma.

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Each teaspoonful (5 ml.) contains: phenylpropanolamine hydrochloride 12.5 mg.; pheniramine maleate 6.25 mg.; pyrilamine maleate 6.25 mg. Side effects: Drowsiness, blurred vision, cardiac palpitations, flushing, dizziness, nervousness or gastrointestinal upsets. Precautions: The possibility of drowsiness should be considered by patients engaged in mechanical operations requiring alertness. Use with caution in patients with hypertension, heart disease, diabetes or thyrotoxicosis. Dosage: Children 1-6, ½ tsp.; Children 6-12, 1 tsp.; Adults, 2 tsp. Administer every 4 hours. Supplied: Bottles of 4 fl. oz., pints.

(Advertisement)



Abstracts, Briefs and Commentaries

THE TINY FLAWS IN MEDICAL DESIGN CAN KILL

The number of patients who have been injured and killed by electrical shocks in hospitals has stimulated several organizations to seek ways to prevent these accidents. Efforts to set safety design standards are being made by such professional groups as the Safety Committee of the Instrument Society of America, the Corresponding Committee of the IEEE, and the Standards Committee of the Association for the Advancement of Medical Instrumentation. In Congress a bill has been introduced in the House of Representatives to create a national commission that would study the quality controls and manufacturing procedures of companies that make medical instrumentation equipment.

The reason for all this concern is the growing number of injuries from malfunctioning and poorly designed equipment. At one midwest hospital, according to Dr. Paul Stanley, Professor of Aeronautics, Astronautics and Engineering Sciences of Purdue University, 40 to 50 patients were shocked in a period of a few months because of a design error in an electromechanical dye injector. Assailing "poorly designed and shoddily built" equipment, Dr. Stanley said: "In some instances circuits have been lifted directly from published articles on the design of medical instruments without verifying the circuit's adequacy for the company's particular application."

However, the responsibility for preventing accidents does not fall entirely upon the manufacturers of equipment. Hospitals, too, must adopt higher standards of safety for electrical circuits in patients' rooms. The use of three pronged plugs and the installation of isolation transformers and alarms that automatically signal an open ground should be mandatory on the wards as well as in the operating rooms.

Van Lawrence, M.D.
Rochester, Minnesota

Gechman, Ronald: Tiny Flaws in Medical Design Can Kill. Electronic Design September, 1967.

SEAT BELT INJURIES

This article points up the type of injury that may occur from the seat belt in a high speed auto accident. The patient with a solid viscus injury may present with shock and hypovolemia, but a hollow viscus injury may be

present in the patient and manifest itself in a more insidious manner, thus allowing precious hours to be lost. Three cases are presented. The authors are careful to point out that this injury is an acceptable risk to the alternate possibility of the rider becoming a hurtling free body following the impact, with its greater inherent danger.

Harrison H. Farley, M.D.
Minneapolis, Minnesota

Porter, Samuel P. and Green, Edward W.: Seat Belt Injuries. Arch Surg 96:242, 1968.

MALLORY-WEISS SYNDROME

Hemorrhage from gastroesophageal lacerations caused by vomiting is known as the Mallory-Weiss syndrome. A review of the literature is presented and three new cases are reported. These lacerations may follow any event that brings about a marked increase in intra-abdominal pressure, such as vomiting, coughing, straining at stool, blunt external trauma, etc. It appears that this syndrome is frequently unrecognized in many patients with self-limited gastrointestinal bleeding. Only those cases requiring surgery or endoscopy have been recognized to date and reported as "rare" examples of Mallory-Weiss syndrome. This syndrome should be looked for in any patient with upper gastrointestinal bleeding and a history of vomiting or straining before bleeding.

Courtesy of References and Reviews
Journal of the American Medical Association

Dobbins, W.: Gastroenterology 44:689, 1963.

SELECTIVE MANAGEMENT OF STAB WOUNDS OF THE ABDOMEN

A ten-year review of stab wounds of the abdomen treated at the Presbyterian-University of Pennsylvanian Medical Center was undertaken to ascertain whether it is justified for those physicians responsible for the care of these patients to be selective in deciding who needs immediate exploration and who may be safely observed.

The authors are concerned in their group of patients who were immediately operated upon, for only 32% proved to have injuries requiring repair. In their group of patients that were closely followed "conservatively,"[20] there were two significant injuries that should have had immediate repair; however, neither of these patients died. The authors are against a program of laparotomy for all patients with abdominal stab wounds.

Comment: More and more articles are mentioning selectivity in the care of patients with abdominal stab wounds. The two reasons given are the high incidence of no significant findings on routine exploration, and the fact that usually these patients present a higher than usual anesthesia risk. The practicing physician should note, however, that the authors stress very frequent detailed examinations in order to diagnose any developing problem. There is still considerable doubt as to the wisdom of this type of program.

Arch Surg 96:292, 1968.

Harrison H. Farley, M.D.
Minneapolis, Minnesota

THE FAT AMERICANS

People, Sir William Osler once observed, are apt to dig their graves with their own teeth. And Americans, say two London epidemiologists in *The*

Lancet, may burrow faster towards posterity than Englishmen.[1]

For after surveying cardiovascular symptoms, smoking habits, blood pressures, electrocardiograms, heights, weights, and skinfold thicknesses of 676 English Post Office workers and 625 similarly employed Americans, they close with this observation: ". . . American excess in ischemic heart-disease is most likely related to the adiposity of the American middle-aged male." Some of their facts on men aged 50 to 59 were these: 7.9 percent of the Americans had symptoms of angina against 4.6 percent of the English; 9.7 percent had symptoms of possible infarction versus 2.4 percent of the English; and Americans' cardiographs showed 7.9 percent with "probable ischemia" and 13.5 percent with "possible ischemia" while the English figures were 2.7 percent and 9.2 percent. Furthermore, those Americans from 40 to 59 had higher blood pressure (135/80 versus 130/78), stood taller (176.5 cm to 172.8 cm), weighed more (82.1 kg to 73.3 kg), and had thicker skinfolds at the triceps (19.0 mm to 8.3 mm) and under the scapula (21.6 mm to 14.6 mm). Because of these measurements and other figures, such as a 50 percent higher death rate from coronaries in the United States than in England and Wales, the epidemiologists indicated fatness as a likely contributing cause of sudden death in America.

One subject our two investigators did not go into is whether Americans eat more or exercise less. Though jogging has emerged as our "in" sport, weight reduction and exercise clubs have sprung up on both sides of the Continental Divide, and men pursue a ball with a liquid center across verdant fields, we still prefer to propel ourselves in the sitting position. The British maintain footpaths across their fields and meadows, but we surface our walking space with concrete to accommodate our cars as we speed home to our bountiful tables. We like our cars big and our concrete wide. It gives us the mobility, the comfort and the time we need to get to our spas, gymnasia, jogging grounds, and golf courses.

Richard L. Reece, M.D.
Minneapolis, Minnesota

Reid, D. D., and Holland, W. W.: An Anglo-American Cardiovascular Comparison. II, 1375, 1967.

JUVENILE DIABETICS

Part of the literature on juvenile diabetes has been reviewed. The favorable immediate prognosis that can be offered today to the new diabetic child is contrasted to that of the pre-insulin era. Nonetheless, vascular complications occurring after relatively few years of the disease point to deficiencies in understanding and possibly to errors in treatment. Examination of current concepts about the etiology of these sequelae and their relationship to past control led to the conclusion that, whereas vascular pathology is probably inherent in the diabetic state, the degree of damage and the consequent loss of function could be modified to some degree at least by maintenance of good control. In this respect, the role of serum lipids and the dietary fat content were reviewed, but definitive conclusions seemed unwarranted. Oral hypoglycemic agents were shown to have little or no place in the treatment of juvenile diabetics. Continued careful observation of patients is needed to improve understanding and management of this disease.

Courtesy of References and Reviews
Journal of the American Medical Association

Belmonte, M. Canad Med Ass J 88:1112, 1963.

SCREENING FOR CUSHING'S SYNDROME

What makes Cushing's syndrome tough to diagnose by laboratory tests? The confusion generated by the many types of tests available? The overlap between valves in patients with and without the syndrome? The careful control needed to give steroids to suppress adrenal function?

All are factors, but the big problem is collecting an accurate 24-hour sample of urine. Because of the human element, the collection of specimens tends to be poorly timed, or to be incompletely collected. These factors make it difficult to screen patients in offices or clinics, and they must be hospitalized to assure accurate tests.

Lately, though, a flurry of papers has appeared that indicate that plasma cortisol levels after a single dose of dexamethasone serve as well as more complex tests.[1-4] The principle is simple. In normal subjects, plasma cortisol is highest at 8 to 9 A.M. and lowest in the evening, whereas cortisols in patients with Cushing's syndrome do not vary much. Also patients with the syndrome, when given dexamethasone, do not usually decrease their cortisol level in the evening, as do normal subjects.

To test for Cushing's syndrome, then, measure the plasma cortisol in the morning and the evening (some consider this check on diurnal variation as optional[2]), give 1 mg of oral dexamethansone at 11 P.M. to midnight, and collect a blood sample at 8:00 A.M. the following morning for plasma cortisol. If the morning plasma cortisol level is suppressed (meaning levels less than 11 μg per 100 ml, 5 μg per 100 ml, 6 μg per 100 ml, 10 μg per 100 ml in the different series), Cushing's syndrome is ruled out.

Richard L. Reece, M.D.
Minneapolis, Minnesota

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3. Seidensticker, J. F., Folk, R. L., Wieland, R. G., and Hamwi, G. J.: Screening Test for Cushing's Syndrome with Plasma 11-Hydroxycorticosteroids. JAMA 202:87, 1967.
4. Sawin, C. T.: Measurement of Plasma Cortisol in the Diagnosis of Cushing's Syndrome. Ann Intern Med 68:624, 1968.

His Nganga* Failed

Nyamyaro:† a MuZezuru aged thirty-eight, came from Marandellas. Three weeks after he became ill, his wife consulted a diviner who told her that his grandmother's spirit wanted beer. Some time before this, when another member of the family was ill, a cow had been sacrificed to the grandmother's spirit, but the final ceremony of mweredzo (beer offering) had been omitted. This had upset the spirit which had shown its annoyance by making Nyamyaro ill.‡

*Nganga—Southern Rhodesian witch doctor.
†Nyamyaro was admitted to a Southern Rhodesian hospital after his nganga failed to cure him.
‡Michael Gelfand: Witch Doctor, 1965.

The Sick In Soul

The sick in soul insist that it is humanity that is sick, and they are the surgeons to operate on it. They want to turn the world into a sickroom. And once they get humanity strapped to the operating table, they operate on it with an ax.—Eric Hoffer.

Special Article

Exercise—the Heart and the Doctor Athlete

A Nine-Year Survey

SERGIUS BRYNER, M.D.*
Palo Alto, California

EXERCISE AS a deterrent to myocardial infarction and death from myocardial infarction aroused little interest in this country at the start of this study, though Europeans were considerably more intrigued. In the last few years the idea has begun to incite dreams of longevity in the minds of a rapidly increasing number of doctors as well as laymen. At the 1967 American Heart Association meeting a substantial segment of papers bore on this question.

Now exercise enthusiasts and patients who have sustained myocardial infarctions, who have angina or positive exercise electrocardiographic abnormalities without angina, are filling our swimming pools, tennis courts, recreation centers, health clubs, ski slopes, mountain trails and the like and are making the bicycle industry prosperous.

The rationale and experimental basis for the belief that regularly-performed sustained-endurance exercise may act as a deterrent to ischemic heart disease has been previously studied with the following observations:

1. Obstruction or narrowing of a major coronary vessel is alleviated by a far richer collateral circulation in exercised than in sedentary subjects.
2. In such exercised subjects an additional coronary obstruction is less likely to be disastrous than in the slothful.
3. Increased fibrinolytic activity is stimulated by and persists for some time after exercise.
4. The potential for oxygen uptake is greater in athletically trained persons than in healthy nonathletic subjects due to the greater stroke volume and A-V oxygen differences in the former. (One might say that maximum oxygen consumption is a measure of the functional ability of the cardiovascular system.)
5. Mild hypertensives trained to become endurance athletes experience after training (for the same workload done before training) a drop in A-V oxygen difference, heart rate and oxygen consumption, and they are able to increase cardiac output to higher levels than before training.
6. Athletes are able to perform the same amount of work as nonathletes with less lactic-acid accumulation (oxygen debt).
7. Statistical studies from prospective programs such as the Framingham Project show that the risk of death or angina from coronary disease in the physically vigorous is approximately one third that in the sedentary population. However, these studies do not assess the reason for the sedentariness of some of the subjects nor the role of obesity.

*Palo Alto Medical Clinic.

The Present Study

A study was begun nine years ago with an annual questionnaire on 112 members of the Northwestern Medical Association. The study was not aimed at the effect of exercise on cholesterol levels, and not enough data on cholesterol was obtained to permit the collection of any significant data.

Period of Observations

Of the 112 members surveyed, 101 were followed through 1967 or died:

69 followed 9 years—1959 to 1967
23 followed 8 years—1960 to 1967

1 followed 7 years—1961 to 1967
8 died

Data from the other 11 were nevertheless sufficient to be used in the statistics tabulated.

Age Distribution

The participants were grouped by their age at the end of the study from Group I through VII as follows:

TABLE 1
Age Range of 112 Subjects in NWMA Coronary Disease Study 1959-67

Group No.	Age Range at End of Study	No. of Subjects
I	< 46	15
II	46 - 50	25
III	51 - 55	36
IV	56 - 60	11
V	61 - 65	17
VI	66 - 70	6
VII	71 - 75	2

Tobacco Consumption

During the course of the study there appeared to be an overall drop in tobacco use from about 41% to about 30% in the nine-year period, a decrease more marked in the older than in the younger age groups. Perhaps in the younger age group the philosophy "it can't happen to me" persists.

Dietary Habits

Roughly one third in each age group reported they followed a diet low in cholesterol and saturated fats.

Low in Saturated Fats and Cholesterol

TABLE 2
Use of Diets Low in Saturated Fats and Cholesterol by 112 NWMA Members 1959 - 1967

Group No.	Number Following Low Saturated Fat Low Cholesterol Diet: At Start Study	Number Following Low Saturated Fat Low Cholesterol Diet: At End Study	Number Abandoning Diet During Study	Number Adopting Diet During Study
I - 15	4	4	0	0
II - 25	7	8	0	1
III - 36	10	10	2	2
IV - 11	4	4	0	0
V - 17	5	6	0	0
VI - 6	2	2	0	0
VII - 2	0	0	0	0
Total	32	34	2	3

Weight Changes

The weight range of this group as a whole revealed no markedly over or underweight members. A few were slightly underweight. The following table shows the weight trend in the group without stating the degree of obesity, since for practical purposes the overweight was always of moderate degree.

TABLE 3
Incidence of Overweight in 112 NWMA Members 1959-1967

Group No.	Number Overweight at Start of Study	Number Overweight at End of Study
I - 15	4	5
II - 25	2	6
III - 36	9	11
IV - 11	0	5
V - 17	2	6
VI - 6	0	0
VII - 2	0	1
Total	17	34

These simple statistics show a rather clear-cut and striking trend in this small aging population of men, in that the incidence of obesity increased by 100%.

Morbidity

Very little nonfatal coronary artery or cardiovascular disease was found in this group.

Infarction

Nonfatal myocardial infarction occurred in one (a very moderate exerciser whose pattern would be classified as somewhere between light and moderate physical activity). This is therefore not a significant case in determining the incidence of ischemic heart disease in the vigorous exercise group.

Angina

Mild angina occurred in one subject who exercises moderately and who, as far as can be determined, no longer experiences the angina. Two other cases of chest pain are reported, both of doubtful significance. Angina with tobacco was reported by only one member, who later died of external causes. Another member reported one single episode of what he interpreted as angina when under great physical stress and threat to his safety.

Hypertension

Mild hypertension has been found in eight members. There has been some talk of exer-

cise as a preventative or cure for hypertension, but this group does not support that contention, since hypertension was not uncommon. It may be significant that all were mild hypertensives; but since four of these eight were classified as heavy or moderately heavy exercisers, a heavy exercise program does not appear to prevent hypertension.

Comments

Physiologists, who are involved in this kind of study, agree that for exercise to stimulate substantial and effective coronary and collateral growth it must be constant, consistent and of an endurance nature which taxes both circulation and ventilation and is accompanied by a sizeable and continuing increase in pulse and respiratory rates. Brief sporadic muscular challenges with no lasting effect on pulse and respiration other than that produced by repeated Valsalva maneuvers do not appear to be an appropriate type of exercise.

In spite of many attempts to acquire detailed data on exercise habits in the questionnaires there were too often answers such as "swim daily," "hunt, ski, fish, tennis and golf," "daily calisthenics," "frequent jogging" and the like, which were impossible to quantitate as to frequency, duration, speed, distance, intensity, etc.

Nevertheless, an assessment was made of each member's questionnaire as accurately as possible and exercise was classified into five categories: Light exercise, light-moderate exercise, moderate exercise, moderate-heavy exercise, and heavy exercise.

The "heavy" type of exercise (squash, tennis singles, very competitive tennis doubles for several sets, fast swimming over substantial distances of 400 yards or more, running, hill climbing, bicycle touring, exercycling against resistance to exhaustion, calisthenics which are long and vigorous, earth-moving type of yard work involving prolonged vigorous activity and the like) five or more times a week with infrequent lapses for illness, medical meetings and the like is challenging and should qualify as satisfactory endurance-type exercise. "Moderate-heavy" exercise may also qualify with some reservations and probably in many cases is also sufficiently vigorous to have a substantial effect on production of coronary collaterals in the presence of obstruction. In this category would be brisk, but not heavy endurance exercise done frequently and regularly or heavy type endurance exercise done less regularly than by those in the "heavy" category. In order for a member to qualify for the two heaviest categories of exercise at the end of the study it was necessary that he perform this type of exercise over a period of at least twelve months without any evidence of angina, syncope or other cardiac symptoms.

Since there is no scientific delineation of the exact amount and frequency of exercise required to rapidly develop generous collateral coronary circulation, one is forced to extrapolate in a rather crude way from animal experimentation and autopsy studies. Follow-up studies on the Vineberg procedures such as those reported by Gorlin do suggest that a substantial amount of coronary collateral circulation can be built up in the myocardium over a period of six months or less.

Some of the groups tabulated here are far too small to have any statistical significance. There has been a general shift away from "light" and toward "heavy" exercise in the group as a whole over the nine-year period of study, the biggest changes occurring away from the "light" and toward the "moderate-heavy" group.

Perhaps the most striking phenomenon is that in the groups studied, age seemed to have very little significance in exercise habits from decade to decade.

The Deaths

The deaths which occurred in this study had little bearing on the outcome of the survey. The ages at the time of death were 42, 43, 45, 50, 54, 55, 63 and 75. Two deaths were due to malignancy and two to external causes; four deaths were cardiac.

One myocardial infarction occurred at the age of 42 in a man who had been overweight for twelve years, who had had a normal EKG one year before, and who did not use tobacco. He had done heavy exercise in high school and college but light thereafter with only spurts of heavy activity (perhaps the worst kind of an exercise program).

Another myocardial infarction occurred at the age of 50 in a man who had smoked 20 cigarettes a day for 30 years and was slightly overweight. His exercise in high school was

heavy, but nil in college and light to moderate thereafter. He engaged in only moderate physical activity for several years prior to his death and was lost track of during the last two years before he died.

One death occurred in a man with hypertensive cardiovascular disease who had advanced heart disease from 1954, including a myocardial infarction, heart failure and severe peripheral vascular disease and who gamely continued to ski hard a few times each year, remaining largely sedentary for the rest of the time. This too would seem to be the worst possible exercise program for anyone — let alone an individual who was already a cardiac. This man did not smoke.

Another death occurred at age 75 in a man who did not smoke and who had mild nonanginal symptoms and electrocardiographic changes between 1964 and 1966, death occurring in 1966. Myocardial infarction was not proven, but death was almost certainly due to myocardial infarction or ventricular fibrillation resulting from ischemic heart disease. His exercise habits were moderate but very regular, consisting of three sets of tennis two or three times a week for six months of the year, swimming two to three times a week three months a year, and skiing when he could. We do not know how hard he swam, but we classify this program as moderate because the level of activity was doubtless not very high and also because it probably was neither year-round nor daily. Nevertheless it is of great interest that this man was able to carry on this exercise program after the occurrence of syncope and electrocardiographic change without developing any angina. The fact that syncope was his only symptom prior to death and that the final episode was also a syncopal attack tempts one to speculate whether the exercise program was vigorous enough to develop sufficient collateral circulation to prevent myocardial infarction and angina but not to prevent a fatal arrythmia due to a partially ischemic area of the myocardium.

At the end of the study 41% of the subjects were in the 2 heaviest exercise groups and presented no adequate evidence of ischemic heart disease except for one in the "moderate-heavy" category who while being symptom free had a "positive treadmill test" about which no further details are proven.

Conclusions

While not offering conclusive proof for the value of frequent, challenging, endurance-type exercise as a deterrent to ischemic heart disease this study gives encouragement and support to the possibility that this type of exercise when properly performed may be of value. Larger prospective studies will have to be completed before a conclusive answer to this question can be obtained; and, ideally, angiographic studies should be available but are not likely to be in the foreseeable future.

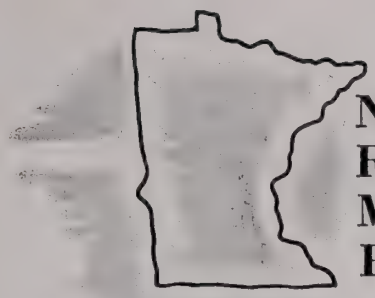
Perhaps the "heavy" group should be studied in other perspectives. Are they a compulsive, unhappy group? Are they as productive as they should be? Are they more neurotic than the less disciplined members of society? Being one of the group myself I have no hesitation in casting these aspersions. It would be of significant interest and value to have a psychological test study of this group of "heavy" and "moderate-heavy" members.

Whether or not the very low incidence of tobacco usage in these groups plays a major part in their continuing good cardiac health remains also for the moment unanswered.

Your Health—Mr. President

It is interesting to note that of the first thirty Presidents the average age at death for the first ten, up to and including John Tyler who died in 1862, is 77.4 years; for the second ten, from Polk to Garfield, 63.7 years; and for the Presidents from Arthur on, 63.1 years. Of the first group, John Adams lived to the age of ninety, three others were in their eighties when they died, and only two, Washington and William Henry Harrison, were under seventy at the time of their death. And this in spite of the epidemics of infectious diseases, the lack of sanitation, and the primitive state of medicine during most of that era! How can one explain the fact that despite all the advances of modern medicine, the Presidents of the twentieth century pre-decease their early predecessors by an average of more than fourteen years?*

*Karl C. Wold, M.D.: Mr. President—How Is Your Health?



NORTHLANDS REGIONAL MEDICAL PROGRAM

REGIONAL PROGRAM FOR HEART DISEASE, CANCER AND STROKE

A New Medical Information System
The Dial-Access Medical Library

1. *A new Information Resource for Minnesota Physicians*

   All physicians in Minnesota will soon have immediate telephone access to a library of authoritative magnetic tape abstracts of a wide variety of medical subjects.

   Northlands Regional Medical Program will join Wisconsin Regional Medical Program to expand Wisconsin's Dial-Access Medical Library and make it available by toll-free telephone transmission to all physicians in both states. The Wisconsin program was developed under the leadership of Dr. Thomas Meyer, Director of the Department of Post-Graduate Education of the University of Wisconsin College of Medicine, and has operated successfully since 1966. Under the new cooperative arrangement Minnesota physicians will participate by producing new tapes to equal the contributions of Wisconsin physicians.

   All physicians in Minnesota will receive a copy of the catalogue and complete instructions by mail. Display units with extra catalogues will be placed in every hospital.

2. *The Medical Library* is a library of five minute magnetic tape abstracts of single topic medical subjects. Each tape is prepared by an expert on the subject, who is identified in the catalog and at the end of the recorded abstract. All recordings are updated annually or oftener so that information is always current.

   The Wisconsin Library now contains 225 single concept tapes. Minnesota Regional Medical Program joins Wisconsin Regional Medical Program to progressively enlarge the library and make it accessible to all physicians in both states.

3. *Dial-Access*

   In-Wats telephone line rental makes it possible for any physician to call the library, toll free, from any telephone, at any time day or night, 365 days a year.

   The library is operated by personnel of the University of Wisconsin Emergency Pharmacy, which is staffed 24 hours a day.

   The physician simply dials the Wats line number, identifies himself, requests his choice of tapes and then listens as the tape is played for him.

   In order to limit use to physicians and to provide a means for evalua-

tion of the efficacy of the program, each caller is asked to identify himself. Service is refused to non-physicians.

4. *Further Telephone Consultation*

   Each tape author has agreed to accept personal calls from physicians for additional consultation whenever anyone desires. (This cannot be toll-free, however.) The additional service to physicians also permits reception of ideas for improvements or additions to the library.

5. *Evaluation*

   The method permits the following evaluations:

   a. Total number of requests, by hour, day, week and month.
   b. Number of requests for each tape in library.
   c. Random sample opinions from physicians using the service (by post-card questionnaire). Such feed-back permits constant up-grading of the library.

6. *Potential Expansion to Para-medical Disciplines*

   The Wisconsin Regional Medical Program is in the process of developing an analogous Nursing Library. Similar programs could easily be developed for other paramedical disciplines.

7. *Future Potential*

   If this system can be expanded to cover the entire field of medicine, it will then constitute a medical encyclopedia which is always up to date and always accessible from any telephone.

   The magnetic tape library can be replaced by a computer data bank when size and need dictate. Printed copy display on cathode-ray tube units with attachments for production of instant hard copy is also possible. Automated cataloguing, indexing, and searching programs can provide amazingly rapid retrieval of desired information from an enormous bank of computer stored information.

This is the first program instituted by Northlands Regional Medical Program to help make the latest in medical care knowledge constantly available to all practicing physicians. We hope and trust that Minnesota physicians will use the system and help us to make appropriate modifications and additions.

Winston R. Miller, M.D., F.A.C.P.
Program Director

Minnesota Medicine Cover Photographs

In order to encourage more physicians to submit color slides for use on the cover of MINNESOTA MEDICINE the competition is being discontinued. The picture editor now invites all physician-photographers to send 35 mm. color slides of suitable subjects for consideration as cover pictures. The format must be horizontal because of printing limitations. Pictures highlighting Minnesota seasons, places, and activities will have an automatic advantage. No limit as to the number of slides sent will be set, but all slides should be individually identified. All slides will be returned. Physicians whose pictures are used as covers will be recognized in MINNESOTA MEDICINE. We can use many more pictures than we have received in the past.

The man who becomes puffed up is ready to fall down.—Forbes Epigrams



Meetings and Announcements

JULY

Summer Camp for Diabetic Children, July 14 through August 4, at Holiday Home, Lake Geneva, Wisconsin. Applications may be obtained from: Diabetes Association, 620 North Michigan Avenue, Chicago.

Postgraduate Course, Ophthalmology, The Stanley Hotel, Estes Park, Colorado, July 8-11. Contact: University of Colorado School of Medicine, Denver.

Air Pollution Medical Research Conference (Sponsors: Denver Medical Society, Colorado Medical Society, American Thoracic Society, American College of Chest Physicians, Colorado State Dept. of Public Health, U.S. Public Health Service, and American Medical Association), Denver-Hilton Hotel, Denver, July 22-24. Info.: AMA Department of Environmental Health, 535 N. Deaborn St., Chicago.

Tenth Annual Methodist Hospital Symposium

The tenth annual symposium, sponsored by the Methodist Hospital medical staff, will be held on Saturday, September 14, 1968, in the Methodist Hospital auditorium.

The subject for this coming year's symposium will be on current concepts and treatment of "shock."

The Minnesota Academy of General Practice has approved this symposium for six prescribed hours of credit.

There is no registration fee for the scientific sessions or the noon luncheon. All physicians are most cordially invited to attend. For additional information please contact Mrs. Audrey Engstrom, medical staff secretary, 929-1313.

Sixth National Cancer Conference

Conference will be held September 18-20 in Denver, Colorado. For full information contact: American Cancer Society, 3702 E. Lake Street, Minneapolis. Phone 722-6614. Subjects to be discussed are cancer of the female pelvis, gastrointestinal tract, skin, neck and head, and lung. Also to be discussed are skeletal tumors, soft part tumors and basic problems and advances in cancer chemotherapy and hormone therapy.

Radiological Technologists Meeting

Minnesota Society of Radiological Technologists will meet October 11 and 12 at the Kahler Hotel in Rochester. Contact: James Powers, R.T., Mayo Clinic, Rochester.

The Minnesota Thoracic Society and the Minnesota Respiratory Health Association announce a second award contest for medical students, interns and resident physicians in Minnesota.

(A) An award of $200.00 is offered for the best paper submitted by a senior medical student or intern on some aspect of respiratory disease, preferably based upon laboratory or clinical investigation.

(B) An award of $300.00 is offered for the best paper submitted by a resident physician based upon clinical or laboratory investigation in the area of respiratory disease.

Further information may be obtained from the Secretary. Entries should be submitted by September 1, 1968 to: David E. Dines, M.D., Secretary, Minnesota Thoracic Society, Mayo Clinic, Rochester, Minnesota.

Minnesota Surgical Society Essay Prize

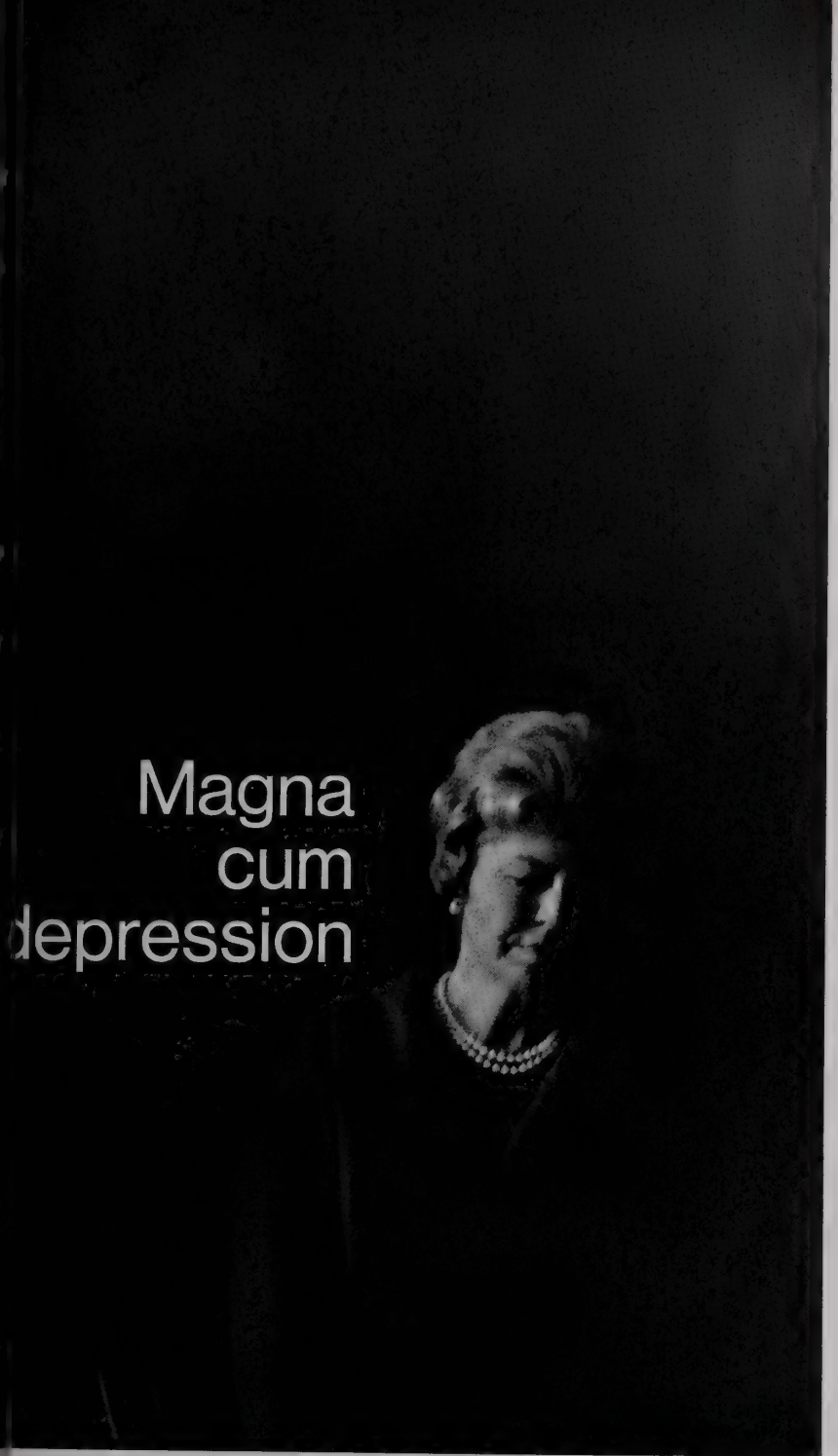
A prize of $500 will be given for the best paper on a surgical subject submitted by a medical student, intern or resident. Papers directed to surgical research and papers on clinical topics are acceptable. Research subjects presented for consideration should be those which clearly have clinical application. The winner will be asked to present his paper at the Fall meeting. Granting of the award is contingent upon the willingness of the author(s) to submit the manuscript for publication in Minnesota Medicine.

Deadline for submission of manuscripts is August 1st, 1968. These should be sent to John F. Perry, Jr., M.D., at the Saint Paul-Ramsey Hospital, 640 Jackson Street, Saint Paul, Minnesota. It is hoped that members of the Society throughout the state will bring this to the attention of house officers and students and encourage them to submit papers.



Tofrānil®, imipramine hydrochloride

Indications: Tofrānil is recommended for the treatment of depressive states of diverse psychopathology.
Contraindications: The concomitant use of this agent and monoamine oxidase inhibiting (M.A.O.I.) compounds is contraindicated. Hyperpyretic crises or severe convulsive seizures may occur. Potentiation of adverse effects can be serious or even fatal. An interval of at least 7 days after M.A.O.I. therapy has been discontinued should be allowed before this drug may be substituted. Initial dosage should be low, increases should be gradual, and the patient's progress should be carefully observed.
Warning: Clinical reports have suggested that there may be a risk of teratogenesis associated with the use of this compound during the first trimester of pregnancy. Unless, in the opinion of the prescribing physician, the potential benefits outweigh the possible risks, it should not be used during the first trimester of pregnancy. Cardiovascular complications, including myocardial infarction and arrhythmias, have occasionally occurred in susceptible individuals. Patients with cardiovascular disease should be given the drug only under careful observation and in low dosage.
Precautions: Since suicide is always a possibility in severely depressed patients and one which may persist until significant remission occurs, such patients should be carefully supervised during early treatment. Some severely depressed patients may also require hospitalization and/or concomitant electroconvulsive therapy. Because of its anticholinergic effect, caution should be observed in prescribing the drug for patients with increased intraocular pressure.
In rare instances, transient cardiac arrhythmias have occurred in hyperthyroid patients and in patients receiving thyroid medication when this compound was added to the regimen.
Imipramine may block the pharmacologic activity of guanethidine and other related adrenergic neuron-blocking agents.
The drug is not recommended at the present time in patients under 12 yea of age.
Adverse Reactions: Dryness of the mouth, tachycardia, constipation, disturbances of accommodation, sweating, dizziness, weight gain, urinary frequency or retention, nausea and vomiting, peripheral neuritis, mild parkinson-like syndrome, tremors, rare cases of falling in elderly patients, confusional states (with such symptoms as hallucinations and disorientation), activation of psychosis schizophrenics and agitation (including hypomanic and manic episodes) which may require dosage reduction



For him, commencement.

For his mother, the beginning of his career may seem the end of hers. The end of feeling needed and useful. The beginning, perhaps, of a pathological depression.

Tofrānil can often relieve the symptoms of her depression. If it can relieve her mental anguish, you may be able to help her graduate into a new and fruitful life of her own.

Tofrānil could be her commencement, too.

Tofrānil® Geigy
imipramine hydrochloride

in depression

The use of Tofrānil in patients receiving M.A.O.I.'s is contraindicated.

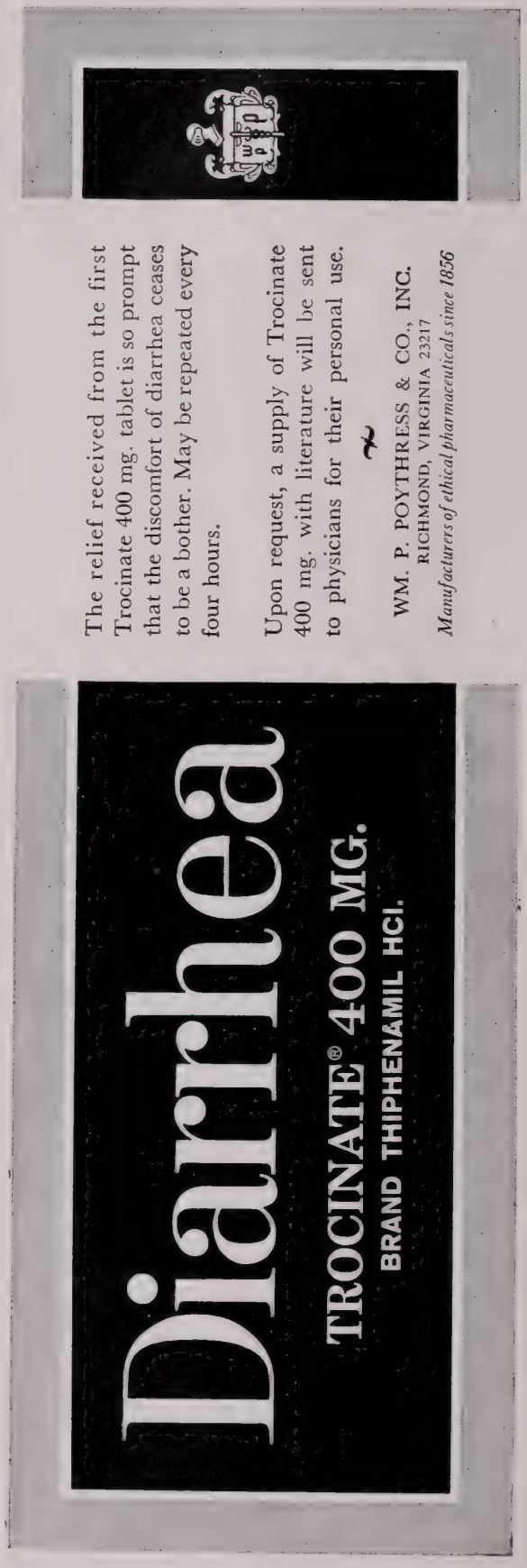
In patients with cardiovascular disease, hyperthyroidism or increased intraocular pressure; in those receiving anticholinergics (including antiparkinsonism agents), thyroid medication or adrenergic neuron-blocking antihypertensive agents; and in those in the first trimester of pregnancy, the precautions discussed in the Prescribing Information should be carefully observed. Although toxic reactions severe enough to require discontinuation of Tofrānil are uncommon, please refer to the Prescribing Information for a description of such instances when discontinuation may be necessary.

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sis, sensitization and skin rash
cluding photosensitization, eosino-
ilia, and mild withdrawal symptoms
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A lag in therapeutic response, lasting from a few days to a few weeks, should be expected. When dosage recommendations are already being followed, increasing the dosage does not normally shorten this latency period and may increase the incidence of adverse reactions.
Availability: Round tablets of 25 and 50 mg.; triangular tablets of 10 mg. for geriatric and adolescent use; and ampuls, each containing 25 mg. in 2 cc. for I.M. administration.
(B)R-46-850-C

For complete details, please refer to the full Prescribing Information.

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Classified

Replies to advertisements with key numbers should be mailed in care of Minnesota Medicine, 375 Jackson, St. Paul, Minn. 55101.

GENERAL SURGEON, Certified, part or full-time association in multi-specialty clinic. Alfred F. Anderegg, M.D., 645-5851, 2500 Como Ave., St. Paul, Minnesota.

WANTED: GP to join clinic serving population area of 12,000. City has new hospital, new clinic building, two nursing homes, new Jr-Sr high school, new swimming pool, rich farming area in Red River Valley. Fishing and hunting nearby; metropolitan city close by. Salary open and partnership if interested. Write or call Warren Clinic, Warren, Minnesota 742-6231, area code 218.

WANTED: General practitioner, to join two G.P.'s well established in north central Minnesota community, 2200 pop., 65 miles from Twin Cities. Excellent office space with lab and X-ray, just opened new hospital, all facilities. Assistantship or partnership. Considerable surgery and obstetrics. Hunting, fishing, golf club. Great opening for interested G.P. WRITE MINNESOTA MEDICINE—381; 375 Jackson, St. Paul, 55101.

INTERNIST AND GENERAL PRACTITIONER wanted to join a five-man clinic group in Minneapolis. Complete laboratory and X-ray with board roentgenologist. Excellent hospital staff associations. Salary arrangement to start with early partnership. Write: MINNESOTA MEDICINE—289; 375 Jackson, St. Paul, 55101.

PRACTICE FOR SALE: Well established general practice in South Minneapolis serving an excellent community, within easy reach of the finest hospitals in the State. Very reasonable, low overhead. Splendid opportunity for solo or partnership practice. Write: MINNESOTA MEDICINE-397, 375 Jackson St., St. Paul 55101.

WANTED: GENERAL PRACTITIONERS, anesthesiologist, Urologist, Obstetrician, Orthopedist, & Pediatrician needed in growing community of 15,000. Service area 25,000. Present 83 bed general hospital. New 100+ bed automated hospital to be completed within 2 years. City has excellent industry, school system, and recreational activities. 45 minutes from Madison or Milwaukee. Future unusually promising. For more information contact: Administrator, Watertown Memorial Hospital, Watertown, Wis.

FOR SALE: Practice—clinic—apartment bldg.—military-exempt town—will retire—14-room clinic-dental suite; 4 apartments. Apartments will retire costs. 2 good schools and churches—good farming area. New large swimming pool—18 hole golf course playable this summer—theatre—bowling alley. 17 miles from St. Olaf Hospital, Austin. Write—P. J. Schneider, M.D., Adams, Minn. 55909.

DIRECTOR OF MEDICAL EDUCATION, full time —Methodist Hospital, St. Louis Park, Minnesota 55426. Contact Mr. Earl Dresser, Administrator or Dr. W. John Dawson, acting director of medical education.

WANTED: General surgeon, G.P. with G.P. residency or internist to join two very busy general practitioners in new, fully equipped office in Chaska, Minnesota, 25 miles from downtown Minneapolis. Accredited hospital. Salary open. Prefer military service completed. Call collect—612-448-2050 Chaska, Minnesota, Drs. Heinzerling and Pistulka.

THREE MAN group in North West Wisconsin Resort, State Conservation and Retirement Area needs two more physicians adequately to serve their practice. Facilities offered are three-room physician suites, X-ray and lab under AMT technician, RN-only nursing personnel. New accredited thirty-two bed hospital and forty-six bed nursing home. Deer and duck hunting, fishing within five minutes of town. Internist most needed; generalists welcomed. Will meet any reasonable salary request. Partnership after one year. Write: MINNESOTA MEDICINE—365; 375 Jackson St., St. Paul 55101.

WANTED: Physician wanted to join three-man group in fast-growing area just thirty minutes south of the Twin Cities. Will practice in a new clinic, new hospital and new nursing home. Salary and terms open. Contact M. H. Hunter, M.D., River's Edge Medical Clinic, Farmington, Minnesota. Telephone (612) 463-7181.

GENERAL PRACTITIONER wanted to join well-established practitioner. New clinic building—90 miles east of St. Paul—city of 14,000. Early partnership with full hospital facilities. Ideal location. L. W. Picotte, M.D.; Chippewa Falls, Wisconsin.

WANTED: YOUNG PHYSICIAN for association leading to partnership with four well-established General Practitioners in fast-growing suburb of St. Paul. Excellent clinic facilities in nearly new, partnership owned, well equipped, medical center building. Contact: A. Eugene Muller, M.D., North St. Paul Medical Center, 2579 East 7th Avenue, North St. Paul, Minnesota 55109.

OPENING IN MT. LAKE, Minnesota for General Practice. Associate practice if desired, adequate vacations, excellent office space, financial help if needed, new 25-bed hospital, nursing home, two old people's homes, over 100-bed capacity in total. Excellent schools and churches. If interested, call collect 427-3515 Mt. Lake, Minnesota or contact Steinle Drug.

FOR SALE: Modern clinic building 44 x 80, brick and block construction. Seven years old, adequate examination, emergency treatment and X-ray rooms, plus private offices, and laboratory rooms. Fully air-conditioned. Located in West Central Minnesota, City of Approximately 5000 population. Write: MINNESOTA MEDICINE-392, 375 Jackson St., St. Paul 55101.

ONAMIA, MINNESOTA, will be needing one or two general practitioners to take over well established practice which will be vacated July 15, 1968. Present doctor leaving area. 3 doctors from nearby towns on staff; group situation strong possibility. Beautiful 31 bed general hospital; 40 bed C&NC unit attached. Almost new clinic bldg. available; dental suite occupied. Area population near 5000 permanent residents; eight to ten thousand summer lake residents and tourists. Hospital located on shores of Onamia Lake; Famous Mille Lacs Lake only two miles distance. Many other desirable lakes for year 'round living close by. Town has 3 industries, Crosier Seminary, Good schools, churches. Two golf courses. Healthy place to live; fishing; hunting; summer and winter sports. Practice has excellent potential. Away from the maddening crowd, yet just a short distance to Minneapolis, St. Cloud and Brainerd. Make the move up to Onamia and Mille Lacs Lake where living is fun—where you'll have something to shout about. Contact M. Engstrom, Asst. Administrator, Community Mercy Hospital, Onamia, Minnesota. Phone (612) 532-3154.

WANTED: G.P. or Internist willing to do some G.P. Twin-towns totalling 12,000 western Minnesota Group now two G.P.'s and one FRCS surgeon. Modern clinic building with eight assistants, X-ray and minor laboratory, 125 bed accredited hospital. Rotating calls one night a week and every fifth week-end. Hunting, fishing, golfing available. Initial salary $1500.00 per month. Oportunity for partnership in one year. Apply to Louis T. O'Brien, M.D., Breckenridge, Minnesota.

SKIING, HUNTING, FISHING and practice of Internal Medicine offered to board qualified or certified internist by 21 man specialty clinic in northern Minnesota. Presently adding new modern facilities to keep up with rapidly expanding economy. Salary first year, shareholder status second year. Reply Russell Anderson, M.D., East Range Clinics, Ltd., Virginia 55792 or call collect, Area Code 218, 741-6244.

WANTED—INTERNIST: Board qualified for four man group in Iowa; two Internists and two Surgeons; own building; Large modern hospital; Midwest shopping and medical center; 30,000; well balanced economy; two hours to three large cities; lake resort 10 miles away; hunting and fishing area; skiing 2 hours away; excellent school system; Junior College; art gallery; superb library facilities. Salary $20,000 to $22,000 depending on qualifications. Early partnership. Write Minnesota Medicine—402, 375 Jackson Street, St. Paul.

SEVENTEEN-MAN Wisconsin group located in college community of 40,000 with excellent hospital facilities is seeking additional associated in the following areas: (1) Internal Medicine, (2) Urology, (3) General Surgery and (4) General Practice. For further information please contact D. R. Griffith, M.D., Midelfart Clinic, Eau Claire, Wisconsin 54701.

GENERAL PRACTITIONER wanted to join academic oriented, well established, congenial Minneapolis group with offices in North and Suburban areas. Full hospital privileges in modern, well equipped hospitals. Practice consists of OB GYN, pediatric, radiology, minor surgical, geriatrics. Liberal vacations and seminars available; Keogh Plan established, life insurance paid by Clinic. Rotating call schedules, full day off. Salary leading to partnership. Write—Minnesota Medicine—410, 375 Jackson, St. Paul, Minnesota 55101.

GENERAL SURGEON interested in some general practice to associate with a 2-man partnership in a rich agricultural community in southern Minnesota. Modern hospital and new clinic building. Hunting, 9-hole golf course, swimming pool. Salary open and full partnership as soon as desired. Write: Minnesota Medicine—405, 375 Jackson, St. Paul 55101.

GENERAL PRACTITIONER urgently needed to join two established General Practitioners in a thriving clinic practice, thirty miles from Minneapolis-St. Paul. Third man is leaving for residency. State military status and references. Early partnership would be preferable. Write: MINNESOTA MEDICINE-406, 375 Jackson, St. Paul 55101.

DOCTOR WANTED in Fairfax Minnesota. Clinic building available. Present doctor leaving. This is an excellent opportunity. Please contact Dr. Glenn Nelson or Leo Keller at Fairfax.

WANTED BY TWO INTERNISTS—a Board Eligible or Board Certified Internist to practice in the Twin City area. Excellent opportunity and early partnership. Write: MINNESOTA MEDICINE-407, 375 Jackson, St. Paul, 55101.

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THE WEST MEDICAL CLINIC has an opening for a General Practice Physician, on October 1, 1968. This is a five man group that conducts a practice near downtown St. Paul and also, has the Airport Medical Clinic at Wold Chamberlain Field, Twin City International Airport. Both clinics have full laboratory and x-ray services with technologists covering both fields.

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The clinic located near downtown St. Paul has a practice limited principally to internal medicine, pediatrics, as well as occupational and industrial medicine. There is only a limited practice of obstetrics and no surgery.

Salary is open and opportunity for partnership is available. Write: West Medical Clinic, 539 W. Seventh Street, St. Paul, Minnesota 55102. Phone: Area Code 612-227-9341.

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Radiology

Resident's Day Research Symposium of the Department of Radiology of the University of Minnesota, Minneapolis, was held May 16. The following medical fellow specialists presented papers describing their research projects:

Dr. James Thomson: "Combination of cytosing arabinoside with x-radiation in the therapy of an experimental mouse brain tumor."

Dr. Robert E. Anderson: "Dosimetry of the North American Field for radiotherapy of Hodgkin's disease using cobalt 60."

Dr. Robert Jeffrey: "Detection of left-to-right cardiac shunts using Freon as an indicator."

Dr. Virgil T. Fallon and Carl Jessen: "Modification of swine skin radiation reaction by topical steroid therapy."

Dr. D. J. Purdie: "Comparison of isotopic and radiographic techniques for renal localization."

Dr. Harry Baltaxe: "Coronary angiography in hypercholesterolemic patients."

Dr. Robert Carlin: "Cardiac papillary muscle dysfunction studied radiographically."

Dr. Eugene Binet: "Radiographic and scintiphotographic studies of cerebral vascular lesions."

Minnesota Medicine at a Glance

Marinesco-Sjögren Syndrome—*Alter and Kennedy* Page 901

A rare syndrome manifested primarily by incoordination, cataracts, and mental and physical retardation is thoroughly analyzed both by case presentation as well as critical analysis of the literature. A reader may gain a comprehensive understanding of the various criteria necessary for diagnosing this condition.

Placental Localization—*Loken et al.* Page 907

An interesting initial study on the localization of the placenta by the use of technetium^{99m}-labelled albumin in 51 patients. There was a 2% error when checked by digital examination at the time of delivery. The technique appears to be of no risk to the fetus and may be of help in diagnosing placenta previa.

Mediastinoscopic Diagnosis of Sarcoidosis—*Johnsen et al.* Page 915

The authors briefly outline the technique of mediastinoscopy and the application of this procedure in certain types of intrathoracic disease. The procedure appears safe in that minimal morbidity and no mortality resulted in this series of 100 patients.

The Grey, Creeping Death

When we examine in retrospect the long line of artists, poets, thinkers and musicians whom today we admire and love, we find many of them living and creating under the shadow of this malignant disease (syphilis), under its curse and its blessing.

The ordinary man might be inclined to close his eyes and turn away in distress to avoid polluting the pure image of those great minds, but the doctor is fascinated by them. For him syphilis is no moral criterion; it does not detract from the greatness of those men. They ran blindly into danger, they were ennobled and then destroyed. They paid the price with their blood and their destruction. One of the most distressing cases is that of Nietzsche. A single, involuntary error, committed under the all-powerful urge of sex, envenomed his body with the dangerous poison that fanned the flames of his genius. In 1889 he entered the Vienna Lunatic Asylum, a helpless wreck, living in a twilight for eleven years until his death. The same fate was suffered by Hugo Wolf, who within a few months composed two or three hundred superlative lieder, generously expending his genius which still enchants us today, until, helpless and oafish, he lay chained to his bed in a padded room. Donizetti, deMaupassant, Baudelaire and many others who produced works of great genius were embraced by the muse but also by syphilis. "Praise be their misfortune, for they have wrested the highest that is humanly possible from their disease." (Romain Rolland.)*

*H. S. Glasscheib, M.D.: The March of Medicine, 1964.

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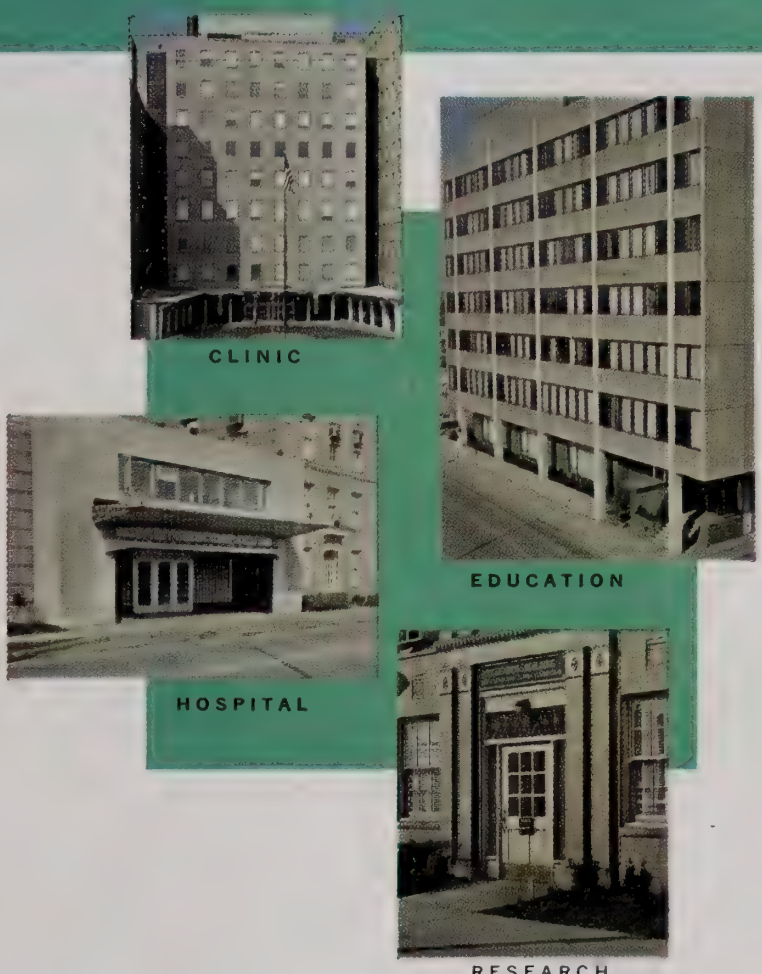
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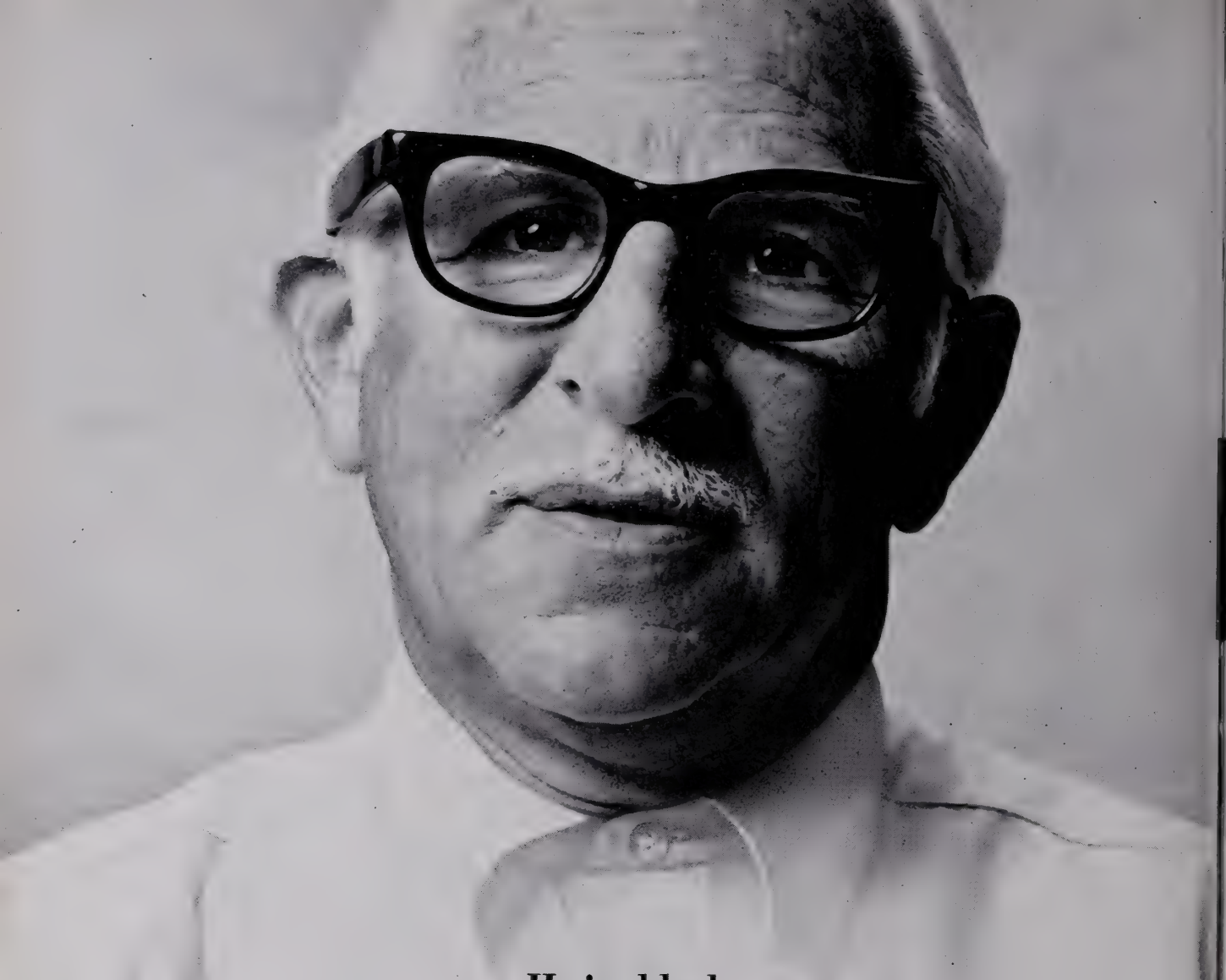
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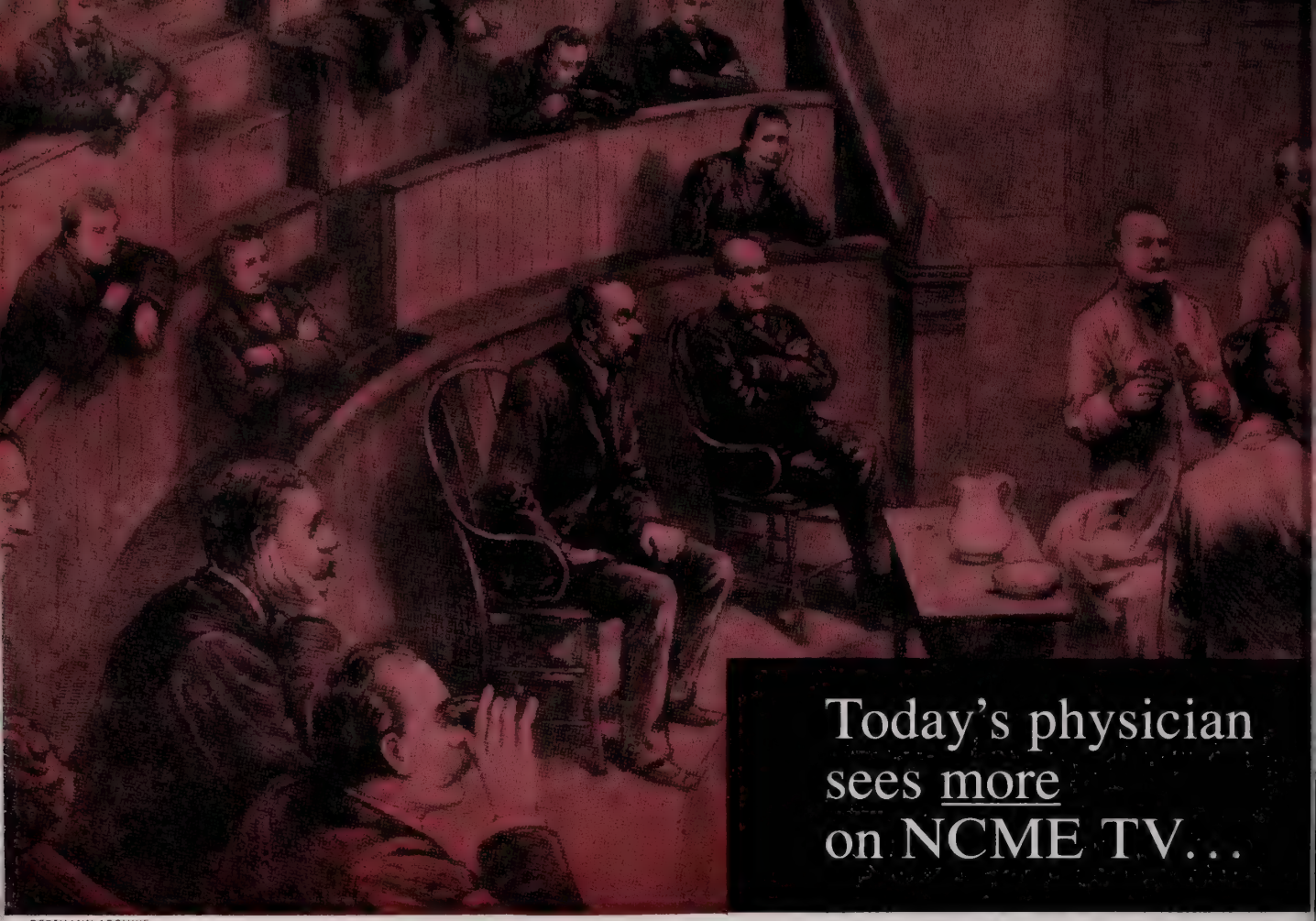
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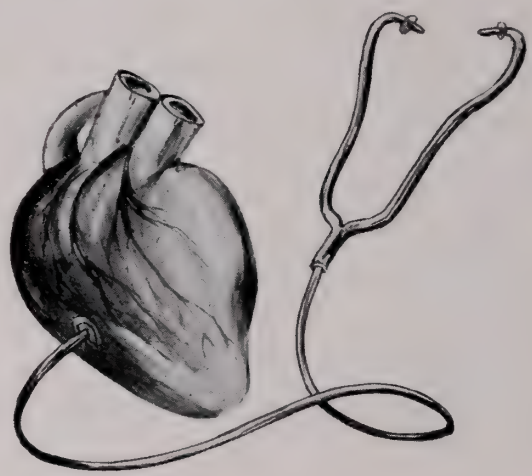
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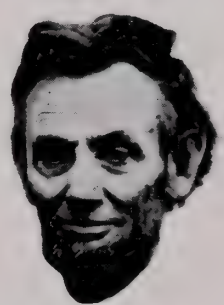
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President's Letter

IN THE INTRODUCTION to the "Practice of Physic" (1798), Richard Temple observes that "The publications of ingenious and observing men, who have paid particular attention to particular diseases, have also furnished us with a happier and more successful mode of treating them."

Such men from the Cleveland Clinic we welcome to these pages of Minnesota Medicine. Long renowned for distinguished medical reporting, contributors from this organization are no strangers to this reading audience. When we have digested and assimilated what they have brought to us, we can perhaps agree with thoughts expressed by Friend in his "History of Physic" (Volume 1). —"Every physician will make, and ought to make, observations from his own experience; but he will be able to make a better judgement and juster observation by comparing what he reads and what he sees together."

The Minnesota State Medical Association, through the medium of its journal, is proud to present this Cleveland Clinic issue.

O. L. N. Nelson, M.D., President
Minnesota State Medical Association

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The Fat Embolism Syndrome

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Cleveland, Ohio

FOR MORE than a century the fat embolism syndrome has stimulated many clinical and experimental studies.[1-4] Its relationship to skeletal and soft tissue injury has been recognized and several cases have been reported.[5] Nontraumatic conditions such as diabetes, burns, blood transfusions,[6] severe infections, poisoning, sickle cell disease,[7] cardiopulmonary bypass[8] and renal homotransplantation[9] may also result in the fat embolism syndrome. Its incidence remains high both on the battlefield and in civilian life. The seriousness of this complication of trauma is generally not appreciated. Controversy continues over the source of the embolic fat. Systemic fat embolism produces a clinical syndrome with characteristic clinical findings and pertinent laboratory test results.[10] Recent advances in the recognition and treatment of fat embolism have contributed to a decrease in morbidity and mortality.

Pathogenesis

For many years the source of the embolic fat was assumed to be intravasation of the fat into the vascular channels at the fracture site. Bone, because of its high fat content, vascularity, and rigidity, provided the ideal setting whereby increased interstitial pressure could force the free fat into vascular channels. In support of this mechanical theory, bone marrow fragments have been found within the lungs.[11]

The physiochemical theory postulates an alteration of the normal plasma colloidal dispersion of chylomicrons, which occurs after trauma, with coalescence of the chylomicrons into larger fat droplets.[12] After trauma the lipid-mobilizing hormone is activated and blood lipid concentrations increase, resulting in a change in the physical state of the blood lipids.[13] Injection of radioiodine (I^{131}) labeled triolein at the ends of fracture sites in experimental animals revealed a slow rate of absorption, demonstrating that the fat absorbed from

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Fig. 1—Common sites of petechial rash.

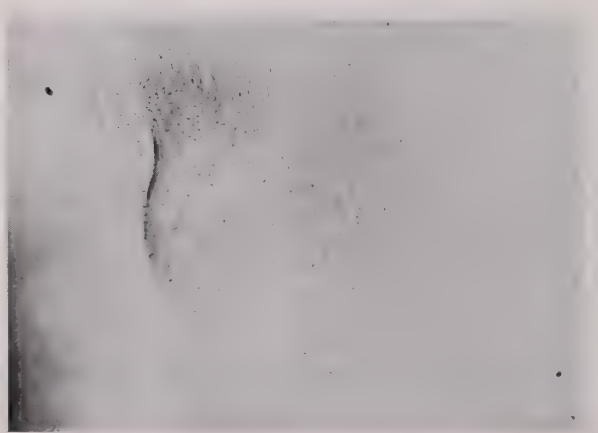


Fig. 2—Petechial rash in axilla.

the site of injury is not the only source of embolic fat.[14]

In the last few years, considerable attention has been directed to the rheology* of blood in the microvasculature (vessels with an internal diameter of less than 100μ). The fluidity of blood is altered by tissue injury, and microcirculatory changes occur. The flow patterns and flow rates of blood cells are notably altered. The changes after tissue injury can be summarized as follows:[15] (1) immediately after injury, aggregation of platelets and chylomicrons occurs, with the formation of white masses; (2) within a few hours after injury, aggregation of erythrocytes occurs; (3) a decrease in the flow rate of erythrocytes occurs in the postcapillary venules and sinusoids. Occlusion or sludging of the erythrocytes may occur. Poor tissue oxygen perfusion with hypoxia or anoxia is the obvious end result.

Therefore, the posttraumatic changes that occur in the microvasculature, in combination with the presence of circulating fat droplets (as a result of alteration of normal lipid stability) provide the physiologic basis for the fat embolism syndrome.

Clinical Manifestations

The fat embolism syndrome is most common in the second and third decades of life, and in the sixth and seventh decades when fractures of the hips are frequent. Ninety percent of the patients demonstrate symptoms within 48 hours after injury, but this time interval may vary from a few hours to four days. An initial latent period without symptoms may occur (Table 1).

Fulminating cases after severe multiple injuries are seldom recognized. Mild cases are frequent but often are not diagnosed. The clinician must have a high index of suspicion to make the diagnosis of the fat embolism syndrome, though its characteristics are specific enough to allow early recognition. Symptoms often begin suddenly and are a manifestation of tissue hypoxia and/or anoxia (signs are dyspnea, cyanosis, disorientation, and delirium). Restlessness and obstreperous be-

*See Test Your Word Score Page 1083.

havior are common. The clinical signs associated with the fat embolism syndrome are a rise in temperature to as high as 103F; tachycardia with a pulse rate of 140; a respiratory rate of 30 to 34. The neurologic examination may demonstrate a changing picture, with occasional extensor posturing and decerbate rigidity. On the second or third day after injury, petechiae often are seen across the root of the neck, in the axillae, and in the conjunctivas (Figure 1). The petechial rash is present for only a few hours and fades rapidly (Figure 2).

Laboratory Findings

Laboratory studies are helpful in the diagnosis of the fat embolism syndrome (Table 2). In approximately 50 percent of the patients, free fat is demonstrated in the urine within the first three days after onset of the syndrome. The urine supernatant fluid must be stained with freshly filtered Sudan III stain and examined for free fat droplets. An unexplained decrease in the blood hemoglobin content often occurs in the early stages of the syndrome. As the fat in the urine decreases, the serum lipase content increases in about 50 percent of the patients. When the diagnosis is suspected, serial examinations for fat in the urine, and the determination of serum lipase content should be started.[16] A roentgenogram of the chest may demonstrate the "snowstorm appearance" that is associated with the fat embolism syndrome (Figure 3). A skin biopsy of a petechial lesion may reveal the presence of intravascular fat. Differential diagnosis includes evaluation of possible acute occult blood loss, drug idiosyncrasies, oversedation, craniocerebral injury, and delirium tremens.

Treatment

Certain general measures should be employed in the treatment of fat embolism. The patient's airway must be maintained; shock must be treated; fluids must be administered; unnecessary transportation must be avoided.

The respiratory failure associated with fat embolism is best treated by mechanically assisting respiration and by the intravenous administration of corticosteroids (100 mg every six to eight hours). Oxygen decreases the tissue hypoxia, and should be given immediately after the diagnosis of fat embolism is suspected. Specific treatment should be directed at lowering the plasma lipid concentrations, preventing platelet aggregation, and improving microcirculatory flow.

Heparin

Injection of heparin, which has specific chylolytic action, will facilitate the passage of chylomicrons into tissues. Heparin activates the lipoprotein lipase and promotes the hydrolysis of the chylomicron to unesterified fatty acid. The fatty acids in solution in the plasma are bound by albumin. The lipoprotein spectrum of the plasma is also altered by heparin, and a change in the physical state of the blood lipids occurs. The anticoagulant action of heparin prevents agglutination of the platelets and improves microcirculatory flow. Small intravenous injections of from 10 to 50 mg of heparin every six to eight hours will achieve a chlolytic effect without the risk of hemorrhage. Heparin used in less than anticoagulant dosage has been beneficial in the treatment of the fat embolism syndrome.[17]

Dextran

Low molecular weight dextran (mean molecular weight of 40,000) is a useful addition to the treatment of the fat embolism syndrome.

TABLE 1
Clinical Manifestations of Fat Embolism Syndrome

Symptoms
1. Dyspnea
2. Restlessness
3. Confusion
Signs
1. Temperature elevation to 103F
2. Tachycardia—rates to 140 or higher
3. Tachycardia—rates to 30 or higher
4. Deterioration in the mental state
5. Changing neurologic reactions
6. Petechiae across the chest, in the axillae, root of the neck, or conjunctivas

TABLE 2
Laboratory Studies, Aids to Diagnosis of Fat Embolism Syndrome

1. Lipuria
2. Serum lipase content (elevation)
3. Blood hemoglobin content (unexplained decrease)
4. Serial roentgenograms of the chest
5. Skin biopsy of petechiae

A profound alteration of posttraumatic microcirculatory flow changes follows its administration.[18] The properties of low molecular weight dextran which influence microcirculatory flow are: (1) expansion of plasma volume; (2) a change in the electric charge of the surfaces of the erythrocytes, improving or increasing erythrocyte negativity; (3) formation of a dextran-fibrinogen complex; (4) a siliconizing effect upon the injured blood vessel wall. Low molecular weight dextran has been shown to be a valuable therapeutic agent in the treatment of retarded flow within the microvasculature.[19] The mortality rate from cerebral fat embolism is less after the use of low molecular weight dextran in a dosage of 500 ml intravenously every 12 hours. Contraindications for the use of low molecular weight dextran are the presence of localized sepsis, renal failure, pulmonary edema, congestive heart failure, severe dehydration, hypofibrinogenemia, and thrombocytopenia.

Summary

Fat embolism produces a clinical syndrome with characteristic clinical findings and pertinent laboratory test results. The incidence and severity of the fat embolism syndrome is great enough to warrant a high index of suspicion. Treatment has become less empiric and more specific with the use of heparin, low molecular weight dextran, and corticosteroids.

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Somapathy

The Illinois College of Somapathy is located at Elgin, Illinois, and its fond father is Dr. C. H. Murray. It appears that this science is devoted to the body suffering. The diagnostician feels around in the place where the nerves emerge from the spinal cord and adjusts them. Then he continues his good effects by applying ice cold, or material heated up to two hundred degrees at the place of adjustment. Here again is an offshoot of chiropractic and osteopathy, with which it is associated in another school. Dr. Murray promises his graduates $10,000 a year if they are successful.*

*Morris Fishbein, M.D., The New Medical Follies, 1927.

Curative Treatment Appreciated

I enjoy convalescence. It is the part that makes the illness worth while.—Shaw

Myocardial Revascularization* with Internal Mammary Artery Implants

DONALD B. EFFLER, M.D.†
Cleveland, Ohio

MORE THAN 1,500 internal mammary artery implant procedures have been performed at the Cleveland Clinic Hospital since April 1962. The decision to utilize Vineberg's[1] revascularization procedure was made after my colleague, Dr. F. Mason Sones, Jr., performed angiographic studies in two patients who had been operated upon five and six years earlier for ischemic heart disease. For each patient the diagnosis of coronary atherosclerosis was confirmed, and in each patient the implanted artery offered collateral support to the impaired coronary circulation. It is now apparent that of all the revascularization operations the internal mammery artery implant procedures have the broadest application to patients with ischemic heart disease.

Selection of Patients

To be considered a subject for revascularization surgery, a patient must undergo complete angiographic evaluation. Sones's[2] technic of selective coronary arteriography makes possible the precise appraisal of coronary arterial circulation with minimal risk to the patient. Ventriculography, which is a simple adjunctive study to coronary arteriography, helps the surgeon to assess the status of the left ventricular myocardium.

Demonstrable Deficit of Arterial Perfusion

The indications for internal mammary artery implant procedures have broadened with increased experience and postoperative evaluation. Stated simply, the patient who is selected for an implant procedure has a demonstrable deficit of arterial perfusion in the left ventricular myocardium. Such a deficit implies that there exists a functional demand for blood. The functional demand for blood, under stress, alters myocardial metabolism, and this results in angina pectoris, which is analogous to the mechanism that produces claudication in the

*See Test Your Word Score Page 1083.

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lower extremities. The commonest site of coronary occlusive disease is in the proximal anterior descending branch of the left coronary artery. Arteriographic demonstration of a significant proximal occlusion plus demonstrable collateral vessels offers the simplest means of localizing the area of functional demand.

Angina Pectoris

Many, perhaps the majority, of patients who have angina pectoris have good heart muscle. This can be determined by left ventriculography, which offers a kinetic evaluation of myocardial function. The normal left ventricular chamber ejects radiopaque dye in characteristic fashion. In contrast, the left ventricle damaged by major myocardial infarction or interstitial fibrosis that results from chronic ischemia, reflects its impaired function by improper contraction, dilatation of the chamber itself, and paradoxic motion. The cineangiographic evidence of impaired myocardial function is quantitative, depending entirely upon the extent and the localization of muscle damage. Frequently the changes will correlate with abnormal pressure readings obtained during catheterization of the left side of the heart. Interpretation of ventriculographic studies is dependent upon the experience and judgment of the observer.

Revascularization surgery by internal mammary artery implants is recommended for symptomatic patients who have demonstrable coronary arterial disease and salvageable myocardium.[3] That one or more infarctions have occurred is not contraindicative to surgical treatment, provided that adequate muscle function remains. Needless to say, the immediate and the long-term prognoses are influenced directly by the extent of irreversible myocardial damage.

Internal Mammary Artery Implant Procedures

Vineberg Technique

The first operations performed by the Cleveland Clinic team consisted of anterior implants according to the basic Vineberg technic.[4] The left internal mammary artery, dissected as a naked vessel from the anterior chest wall, was implanted in the anterior aspect of the left ventricle. Use of the naked artery, and a relatively short myocardial tunnel, limited the effectiveness of this procedure and restricted its use to those patients whose perfusion deficit was confined to the anterior wall of the left ventricle.

Sewell Pedicle

In early 1964, the Sewell[5] pedicle implant procedure was given clinical trial. Sewell's technic utilizes a long pedicle consisting of the internal mammary artery, its accompanying vein, interconnecting vessels, plus muscle, fat, and fibrous tissue. With increasing experience it became apparent that the naked artery of the Vineberg technic offered a lower-risk operation, but the bulky pedicle of the Sewell technic offered a more effective source for revascularization.

Vineberg-Sewell Implant

Combining the best features of the Vineberg and the Sewell approaches, the Cleveland Clinic team utilizes the Vineberg-Sewell implant, which may be applied to any region in the left ventricle where perfusion deficit exists.

A median sternotomy incision permits utilization either of the left or of the right internal mammary artery, or of both arteries. This approach has broadened the indications for implant procedures in patients who have ischemic heart disease. When an anterior perfusion deficit is demonstrable, either the right or the left internal mammary artery may be implanted. When the deficit exists on the lateral and diaphragmatic aspect of the left ventricle, the left internal mammary artery offers an available means for implantation. In so-called "triple vessel disease," where the perfusion deficit is almost universal in the left ventricle, a bilateral implant procedure is performed with a single operation: the right internal mammary artery is placed in an anterior tunnel, the left in a lateral and posterior tunnel.

On occasion, an implant operation is performed as a complementary surgical procedure. Patients who undergo resection of a ventricular aneurysm may benefit by a laterally placed implant. Direct attack upon a segmental obstruction of a dominant right coronary artery may also be augmented by an implant on the anterior wall of the left ventricle.

It is now apparent that the potential for internal mammary artery implant procedures and the variety of operations that utilize this basic approach are greater than originally anticipated. Either internal mammary artery can be utilized for implantation procedure, and any area of left ventricular myocardium is accessible for implantation.

Postoperative Evaluation

The outcome of a revascularization procedure for ischemic heart disease is not determined just from survival and subjective relief. Those who recall an earlier and discredited era of coronary artery surgery know that objective evaluation of the postsurgical patient is essential. Modern coronary artery surgery begins and ends with arteriography. This invaluable procedure offers precise evaluation of the potential patient who may undergo revascularization surgery, and is the only means of establishing proof that the result is a success or a failure.

Evaluation of an internal mammary artery implant procedure is best undertaken one year or longer postoperatively. Arteriography (of internal mammary artery implants) prematurely obtained provides inconclusive data. After one year the psychologic factors are less likely to influence subjective appraisal. Objective analysis by direct opacification of the implanted vessel is feasible, as maximum collateral growth will have occurred.

Results

Critics of revascularization surgery state that available reported series of surgically treated patients are not controlled and that surgical benefit in relation to the natural history of disease is not apparent. Experience at the Cleveland Clinic, less than six years since its beginning, constitutes a developmental period in revascularization surgery in which new diagnostic procedures and relatively new surgical procedures have been combined. An initially timid attitude has gradually given way to one of increased confidence and aggressiveness. The diagnostic and the surgical technics remain in a state of evolution, as members of the medical-surgical team strive for improvement and refinement. Evaluation of surgical results must take into account the preoperative status of the individual, then the success or failure of the implant procedure itself. In addition, the stability or the progress of the patient's basic, underlying coronary arterial disease must be considered. It is unlikely that any revascularization procedure, even eminently successful, will halt the atherosclerotic process itself.

Evaluation of an implant procedure requires direct opacification of the involved internal mammary artery. Complete surgical failure demonstrated by total occlusion of the implanted vessel has occurred in approximately 8 percent of those patients who underwent evaluation studies. In 92 percent of those patients who have undergone postoperative arteriography, the implanted artery is patent. In reporting the results obtained by coronary artery surgery it is difficult to avoid oversimplification. The presence of a patent internal mammary artery within the myocardial tunnel does not in itself imply successful revascularization. At the present time, results based upon internal mammary arteriography are roughly classified as patent or closed. The latter classification is obvious and needs no clarification. The patent implant is listed in one of two categories: Type A—the implant with demonstrable collateral branches to identifiable segments of the coronary circulation, and Type B—the implant without demonstrable side branches.

Demonstrable Collateral Branches

Type A: The ideal implant as determined by arteriographic study shows communication to the proximally obstructed coronary artery. The best results indicate that collateral communications are an extension of the side branches arising from the implanted vessel. Contrary to earlier beliefs, new vessels do not seem to be formed from the implant, although the possibility that they could so form is recognized.

Retrospective evaluation of the preoperative arteriograms suggests that the best implant results are those in which the affected major coronary artery was obstructed more than 90 percent of the luminal caliber and was supported by demonstrable collaterals from adjacent major vessels. Arteriographic demonstration of a direct communication between a

patent implant and an identifiable coronary artery is accepted as proof that revascularization has been accomplished in this particular area of myocardium.

No Demonstrable Collateral Vessels

Type B: Thirty-five percent of patent implants show no demonstrable side branch collateral vessels. In some implants the contrast medium is temporarily suspended within the implant and remains so for several successive heartbeats. In other implants the contrast medium runs off quickly and creates a myocardial blush and opacification of the great coronary vein. Arteriographically, Type B is a much less attractive implant than the one with demonstrable side branch communications. There appears to be some clinical correlation in regard to those patients who demonstrate the Type B patent implant; little benefit is correlated with slow arteriographic runoff, whereas appreciable improvement in symptoms is correlated with a definite myocardial blush. Retrospective analysis suggests that the Type B implant is more likely to result when the involved coronary artery was less than 90 percent obstructed and when collateral support from adjacent coronary vessels was not apparent.

As the volume of postoperative studies among the surviving patients increases, individual observations are made that enhance our understanding of the concept of the internal mammary artery implant and its clinical potential. Not infrequently, a progress study will prove that a major coronary artery has become totally occluded. Often a late progress study will demonstrate that total occlusion has occurred in a region where major infarction would logically follow—under which circumstances the presence of a functioning implant would suggest that the patient has received the desired protection that true revascularization should provide. It is also apparent by comparison of the preoperative and postoperative coronary arteriograms that the best implants result when functional demand is greatest and the involved myocardium is salvageable. This observation has prompted us to accept, for surgical treatment, patients with much more extensive disease than we would have considered four or five years ago. The change of attitude is based upon the observation that the greater the functional demand, the more likely a desirable implant will result; this extension of operative indications is accompanied by the inescapable fact that the initial surgical risk will be increased.

Summary and Conclusion

There is little doubt that Vineberg's hypothesis has been substantiated by the clinical experience of the Cleveland Clinic surgical team. True revascularization of ischemic myocardium can be provided by a properly executed internal mammary artery implant procedure. Proof of this has been established repeatedly by postoperative internal mammary arteriography.

Selection of the patient who should undergo an internal mammary artery implant procedure requires precise evidence that a perfusion deficit exists in the left ventricular myocardium and that the involved muscle is salvageable. The best results are obtained in those patients who have increasing angina pectoris and whose coronary arteriograms demonstrate nearly total or complete obstruction of a major coronary artery, with demonstrable collateral support from adjacent vessels.

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I tremble for my Country when I reflect that God is just.—Thomas Jefferson

Clinical Emergencies Due to Bacterial Infection

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SOME BACTERIAL infections produce clinical emergencies. The situation is acute; the period of potential reversibility is short; and the prognosis is guarded. Prompt recognition and institution of treatment, close observation, and intensive care may be required to prevent death or serious permanent disability. Often it is necessary to initiate antibacterial therapy on the basis of a presumptive etiologic diagnosis after suitable bacteriologic smears have been obtained and cultures have been started, but before the responsible organism is definitively identified. Use of potentially toxic antimicrobial drugs may be warranted when they are known to be significantly more effective than alternative ones against the suspected pathogens. We have limited this discussion to selected bacterial infections that may produce life-threatening emergencies. These include bacteremic shock caused by gram-negative bacilli, acute bacterial meningitis, fulminating meningococcemia, acute bacterial endocarditis, and staphylococcal enterocolitis.

Shock Associated With Bacteremia Due to Gram-Negative Bacilli

Bacteremia due to gram-negative bacilli now appears to be second only to hemorrhage and myocardial infarction as a cause of shock in hospitalized patients.[1] The mortality rate of this type of bacteremic shock ranges from about 40 to 90 percent. Early in this complication, patients may have fever, warm skin, rapid bounding pulse, and hypotension; later more overt signs of shock with generalized vasoconstriction may develop.[2] Pathogens most frequently isolated include *Escherichia coli, Klebsiella-Enterobacter, Pseudomonas, Proteus,* and *Bacteroides.* Polymicrobic infection is not rare. The usual sources of bacteremia are infections of the genitourinary tract, peritoneal cavity, biliary passages, gastrointestinal tract, respiratory tract, and skin.

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Pathogenesis

Bacteremic shock due to gram-negative bacilli often develops in patients receiving intensive medical or surgical therapy for other serious or life-threatening diseases. These diseases and therapies may be of paramount importance in the pathogenesis and eventual outcome of bacteremia due to endotoxin-producing gram-negative bacilli.[1] Among the major underlying conditions are obstruction of the urinary or biliary passages, malignant neoplasms, hematologic disorders, diabetes mellitus, hepatic cirrhosis, third-degree burns, and complications of pregnancy. In about one half of these patients, bacteremia develops after a surgical or instrumental procedure on the genitourinary, gastrointestinal, or biliary tract. Occasionally bacteremia due to gram-negative bacilli has resulted from infection at cutdown sites or from transfusions with contaminated blood.

Management

Successful management of bacteremic shock depends upon early eradication of infection and restoration of adequate tissue perfusion. This is a typical example of a clinical situation wherein it is necessary to initiate antimicrobial therapy without delay after suitable specimens of blood, body fluids, and exudates have been obtained for bacteriologic studies. Results of cultures of extravascular sites of infection (e.g., urine, operative sites), obtained during the period of observation before the onset of bacteremia, may provide a clue to the identity of the causal organisms. Certain clinical features may also suggest a causative organism. For example, *Pseudomonas* may be suspected in patients with ecthyma gangrenosum,[2] third-degree burns, or serious hematologic diseases, particularly if there is agranulocytosis; this suspicion is heightened when the patient has had predisposing antibiotics, adrenal glucocorticoids, and cytotoxic chemotherapeutic agents.[3] When there is no such clue to the identity of the organism, but bacteremic shock due to some type of gram-negative bacillus is suspected, some physicians prefer to administer combined therapy with kanamycin and chloramphenicol until the results of cultures are available. If the response to therapy in from 12 to 24 hours appears inadequate, the regimen may be altered to include polymyxin B or colistin. When the clinical picture suggests *Pseudomonas* infection, some clinicians prefer to administer polymyxin B or colistin conjointly with kanamycin until the results of bacteriologic cultures are known. However, one should be aware of the toxic effects shared by the polymyxin preparations and kanamycin, such as nephrotoxicity and a curariform reaction, and possible enhancement of their occurrence on their conjoint usage. In patients with renal insufficiency, kanamycin, colistin, and polymyxin B must be given in reduced dosage. In addition to antimicrobial therapy, surgical drainage of abscesses, or relief of obstruction of viscera may be required for control of infection in some patients.

Hemodynamic Derangements

Recent studies[4-6] have disclosed wide variations in hemodynamic derangements in patients whose disorders are diagnosed as bacteremic shock. Some patients have had evidence of a disturbance in peripheral vascular regulation, others hypovolemia, and still others cardiac defects. Accordingly, restoration of adequate tissue perfusion depends upon precise identification of the sequential hemodynamic abnormalities in individual patients with shock. When hypovolemia is a contributing factor (e.g., postoperative fluid losses, peritonitis, third-degree burn), expansion of blood volume may restore cardiac output and adequate tissue perfusion. The central venous pressure may be used as a guide to therapy. Sequential determinations of the blood volume may also be desirable. Volume expansion may be continued as long as the central venous pressure does not rise appreciably above 10 cm. of water and physical signs of heart failure do not develop. In patients with normal or low central venous pressure and shock that is not precipitated by obvious volume depletion, expansion of the blood volume with a rapid infusion of dextran may augment cardiac output and improve the circulatory status.[7] When the central venous pressure is elevated or rapidly rises to abnormal levels after infusion, fluid intake should be restricted and cardiac inotropic agents may be indicated. Vasopressor agents,

such as metaraminol and levarterenol, are now being administered less frequently to patients with bacteremic shock. These agents may be beneficial in some patients with shock who do not have hypovolemia, especially if there is little evidence of reflex vasoconstriction. Isoproterenol has been efficacious in some patients with bacteremic shock who do not respond to blood volume expansion and administration of vasopressors.[8] The value of adrenal glucocorticoids and alpha-adrenergic blocking agents in the treatment of bacteremic shock remains controversial.

Acute Bacterial Meningitis

Meningitis should be considered in patients with a history of infection of the upper respiratory tract, followed by vomiting, headache, lethargy, mental confusion, or stiff neck.[9] Diagnostic lumbar puncture should not be delayed in febrile patients who are confused or comatose. It is important to recall that newborn infants with purulent meningitis frequently exhibit a nonspecific illness without fever or nuchal* rigidity.[10]

Purulent meningitis can be caused by any one of a wide variety of bacteria. Accordingly, microscopic examination of the stained spinal fluid sediment should be performed before selection of initial therapy. Furthermore, certain clinical data also provide important clues to the most likely pathogens. If no organisms are detected on the initial spinal fluid smear, these data serve as the sole basis for selection of antibacterial therapy while awaiting the report of bacteriologic cultures.

Neonatal Meningitis.

In infants less than two months of age, enteric gram-negative bacilli, *Streptococci* and *Staphylococci* are the bacteria most commonly responsible for purulent meningitis.[10] If no organisms are observed on the initial smear of spinal fluid of an infant with purulent meningitis, kanamycin and ampicillin may be administered until the identity of the organism is known. If there is clinical evidence suggestive of a possible staphylococcal infection (e.g., furunculosis), methicillin may be administered conjointly with kanamycin until bacteriologic data are reported.

*See Test Your Word Score Page 1083.

"Nonhospital"-Acquired Meningitis in Children and Adults

In patients more than two months of age, *Hemophilus influenzae, Pneumococci* and *Meningococci* account for the majority of cases of bacterial meningitis acquired outside the hospital.[10] In children between two months and six years of age, *Hemophilus influenzae* is the most common pathogen. In children older than six years of age and adults, *Meningococci* and *Pneumococci* are the usual causal agents. *Pneumococci* are most commonly responsible for nonepidemic bacterial meningitis in patients more than 50 years of age. Meningococcal meningitis is the only type that occurs in epidemics. Petechial or purpuric skin lesions frequently develop in patients with meningococcal meningitis, but rarely with meningitis due to other bacteria[9] or to viruses.[10] Recurrent episodes of bacterial meningitis most frequently are due to *Pneumococci* or *Hemophilus influenzae,* but other organisms may be involved. Recurrent episodes of bacterial meningitis are often associated with congenital or acquired communications between the central nervous system and the external environment, persistent parameningeal foci of infection, or defective immunologic mechanisms of the patient.

Ampicillin has been described[11] as being as effective as penicillin G in the treatment of pneumococcal and meningococcal meningitis, and as effective as chloramphenicol in meningitis due to *H. influenzae.* Consequently, in patients more than two months of age, ampicillin now appears to be the drug of first choice for the initial therapy of purulent meningitis not acquired in the hospital. However, ampicillin should not be given to patients who are known to have hypersensitivity to one of the penicillins. In patients with known hypersensitivity to the penicillins, chloramphenicol might be administered as an initial agent when no organisms are detected on the pretreatment smear of the spinal fluid. Some of the possible alternative antibiotics in regard to meningococcal meningitis include erythromycin, tetracycline, or chloramphenicol; in regard to *Hemophilus influenzae* meningitis, or pneumococcal meningitis, chloramphenicol. The usefulness of the sulfonamides in initial therapy of purulent meningitis is limited by the fact that some

strains of *Meningococci* are now resistant to these agents.

Hospital-Acquired Meningitis.

Purulent meningitis acquired in the hospital is frequently due to *Staphylococci* or enteric gram-negative bacilli.[10,12] Meningitis occurring after lumbar puncture often is due to *Pseudomonas.*[13] In patients with *Pseudomonas* meningitis, the spinal fluid may exhibit a greenish fluorescence under ultraviolet light, and this finding may permit anticipation of the subsequent bacteriologic diagnosis.[13]

When no organisms are observed on the initial smear of the spinal fluid of patients with hospital-acquired purulent meningitis, we prefer to initiate therapy with methicillin and kanamycin until the results of cultures are available. In patients with meningitis due to *Pseudomonas,* it may be necessary to administer intrathecal therapy with polymyxin B.

Fulminating Meningococcemia

The presenting manifestations of fulminating meningococcemia may be fever, purpura, delirium or coma, and hypotension. Evidence of meningitis may or may not be present, and death may occur in a matter of hours. Recommended antibacterial therapy is identical to that described for meningococcal meningitis. It is now known that in the shock syndrome associated with meningococcemia (Waterhouse-Friderichsen syndrome) administration of adrenal glucocorticoids and vasopressors has not improved survival rate.[14] Recent evidence indicates that cardiac failure secondary to myocarditis is an important factor in the pathogenesis of meningococcal shock.[15] Therapy with rapid-acting cardiac glycosides and isoproterenol appears to be beneficial.

Acute Bacterial Endocarditis

Some patients with acute bacterial endocarditis may exhibit a fulminating illness with hectic fever, chills, multiple septic emboli, the appearance of new or changing heart murmurs, and congestive heart failure. Death or irreversible cardiac damage may develop rapidly when this condition is not recognized and treated promptly.[16] In patients suspected of having acute bacterial endocarditis, two or three pretreatment blood cultures should be obtained at hourly intervals, and then therapy should be initiated without delay.[17] Since more than 80 percent of cases of acute bacterial endocarditis are now caused by *Staphylococci,*[18] antistaphylococcal therapy should be administered unless some clinical clue strongly suggests the *Pneumococcus, Enterococcus* or some other species.[17] Maximal doses of a penicillinase-resistant penicillin should be given. Cephalothin or vancomycin may be administered to patients with known hypersensitivity to the penicillins. Cephalothin has been well tolerated by a majority of patients with known hypersensitivity to the penicillins; however, it should be given cautiously to those patients because allergic reactions have occurred. Vancomycin may be the preferred agent for treatment of serious infections due to occasional strains of *Staphylococci* that are not susceptible to the penicillinase-resistant penicillins or cephalothin.[19] Vancomycin must be given in reduced dosage if renal insufficiency is present.

Staphylococcal Enterocolitis

The presenting manifestations of staphylococcal enterocolitis may be a catastrophic illness with fever, abdominal distention, vomiting, profuse diarrhea, oliguria, and shock. It occurs in postoperative patients or in other persons who have been receiving broad-spectrum antimicrobial therapy. On examination of gram-stained smears, the feces or vomitus is found to be teeming with gram-positive cocci almost to the exclusion of other organisms. The mortality rate of staphylococcal enterocolitis has been high when treatment was not initiated at the time of the clinical diagnosis. Management consists of discontinuation of antibiotics the patient had been receiving, initiation of measures to restore the blood plasma volume, and administration of an antistaphylococcal antibiotic. Oral therapy with vancomycin is considered to be the preferred method of treatment for staphylococcal enterocolitis.[20,21] In fulminating cases, when oral medication cannot be retained or extraintestinal spread of the infection appears likely, parenteral therapy may be required. Under these circumstances, a penicillinase-resistant semisynthetic penicillin, cephalothin, or vancomycin should be employed.

Comment

The clinical spectrum of symptomatic bacterial infection ranges from benign, self-limited illness to rapidly lethal disease. Some factors contributing to the severity of an infection include the number and virulence of infecting organisms, the anatomic site of involvement, and the status of defense mechanisms of the host. Depending upon the etiology, the severity, and the clinical course of an infection, and upon special circumstances of the patient, the responsible physician must decide whether antimicrobial therapy should be initiated, withheld, continued, modified, changed, or discontinued. When confronted with a patient with a fulminating infection, prompt and decisive action is required to prevent death or serious permanent disability. Often it is necessary to initiate antibacterial therapy on the basis of a presumptive etiologic diagnosis *after* suitable bacteriologic smears and cultures have been obtained and before the causal agent has been definitively identified. Knowledge of the location of infection and the circumstances involved in its development will assist the physician in formulating a presumptive etiologic diagnosis. Knowledge of the antimicrobials that are likely to be effective against the suspected pathogens will provide a rational basis for selection of therapy until the results of bacteriologic cultures and in-vitro susceptibility tests are available.

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Eponyms and Such

They do certainly give very strange and new-fangled names to diseases.—Plato

Novel Use for a Trombone

I was driving along in the sleigh behind Billy one moonlit, cloudless, exhilarating night. . . . The only sound was the tinkle of sleigh bells. As I approached the lonely farmhouse to which I had been summoned, I thought I heard a curious distant sound, but it was not immediately repeated. Billy and I drew up near the house, and as I climbed down from the sleigh, I heard a sudden, terrifying roar. For a second my heart stood still. It sounded to me exactly like an angry bull, and I had seen too many horrible gouges inflicted by infuriated bulls not to regard that animal with respect. I wondered if he might be loose.

I went into the farmhouse—rather fast, I should imagine—and was met by an aged, foreign-looking woman. Suddenly, another roar! To my astonishment, the blasts came from within the farmhouse walls.

"What's all the noise?" I asked.

The mother answered in broken English. "Oh, that's my daughter."

I followed the woman and the unearthly noise, to a rear room lit by an oil lamp. On the edge of the bed, which occupied most of the small chamber, sat an immense girl, about nineteen years old. . . . She held an extra large trombone to her puffed lips, and with a mighty heave she blew out a bass note resembling the roar of the angry bull I thought I had heard. She continued blasting at interals of about a minute.

Between blasts I found out what it was all about. The mother explained that it had been the custom in the family for many generations. When labor began, instead of holding her breath or crying with spasmodic pains, the expectant mother gave vent to her sufferings with a powerful gust of wind through the trombone. Not only did it relieve the agonies of muscular contractions, but also served the purpose of forcing the baby toward the outlet. I could see how it would push the diaphragm down and exert pressure on the abdominal muscles, thus promoting delivery; but I fail to see why a trombone, of all musical instruments, had to be selected.

The girl baby born that unhappy night I hope will have more compassion for her obstetrician than her mother had for me.*

*Joseph A. Jerger, M.D.: Doctor—Here's Your Hat! 1939.

Abdominal Thoracic Syndrome

Numerous upper intraabdominal conditions may cause symptoms that seem referable to the thorax, and those which appear to be abdominal in origin may arise from intrathoracic lesions, such as pneumonia, emphysema, or perforation of the lung. A subphrenic or a huge intrahepatic abscess pointing upward may cause a sequence of confusing symptoms and findings. Many symptoms of suspected gastrointestinal origin have subsequently been found to be due to coronary artery sclerosis.

Another confusing thoracoabdominal relationship is the occasional need of differentiating coronary occlusion and perforated peptic ulcer. In cardiac or other intrathoracic conditions, pain may be referred to the abdominal area due to reflex spasm of abdominal arteries or enlargement of the liver. A common example of reflex organ relationships is the action of a diseased gallbladder with cholelithiasis serving as a trigger mechanism to increase the frequency of coronary artery pain.

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Hoeber Medical Division, Harper and Row, New York

Transplantation of Kidneys from Cadaver Donors

Clinical Results

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INTERMITTENT HEMODIALYSIS and renal transplantation have dramatically altered the treatment that is possible for the patient who has clinically terminal renal insufficiency. These forms of therapy, though, are not available to all patients who need them, because of an insufficient number of hemodialysis and renal transplant programs at hospitals and medical centers, a lack of adequate financial support, and a shortage of donors of kidneys.

At the Cleveland Clinic Hospital we performed our first renal transplant in January 1963, and as of October 1, 1967, 162 transplants have been performed on 139 patients. The source of kidneys in 117 renal transplants was cadaver donors. Among the advantages of using kidneys from cadaver donors is the opportunity to use both kidneys in two separate recipients, which we have done on 31 occasions to date. The one-year survival rate in this group of patients is 48 percent. It is this experience which comprises this report.

Selection and Preparation of Recipients

The selection and preparation of recipients have been discussed in a previous publication.[1] Bilateral nephrectomy was performed on nearly all the patients before transplantation. Initially, splenectomy and thymectomy were performed on randomized patients. We no longer perform thymectomy, but perform splenectomy on all prospective recipients. *The spleens obtained are used for the production of antilymphocytic globulin in horses.* After recovery from the operative procedure the patient lives near the hospital and is maintained on intermittent hemodialysis as an outpatient. The waiting period for a suitable cadaver donor is variable, but the recipient must be readily available.

Cadaver Donors

Although the results obtained in renal transplantation have been better using live donors,[2]

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unfortunately a suitable live donor is often not available for the patient dying of renal insufficiency. A number of recipients of various blood groups are maintained on the hemodialysis program to afford some selection of a recipient when a suitable cadaver donor becomes available.

Blood Group Compatibility

At the present time, major blood group compatibility affords the only criterion used in the selection of a suitable recipient for a cadaver donor, since time is usually too short to allow for serotyping of leukocyte antigens.[3] In a few potential cadaver donors, such as those with irreversible brain damage, there may be sufficient warning of ensuing death to obtain a blood specimen from the donor and to send it to Los Angeles for serotyping. All potential recipients waiting for cadaver donors have been previously typed, and the best recipient for the particular donor can be selected by the leukocyte serotyping technic of Terasaki.[3] Availability of serotyping services in close proximity to the transplant center, and improvements in the speed with which the serotyping can be done will make this method of selecting recipients for cadaver kidneys more practical in the future.

Securing suitable cadaver donors requires the close cooperation of all services in the hospital. When a patient is gravely ill, a member of the renal transplant team is notified, so that the suitability of the patient as a possible cadaver donor can be determined. In general, we have excluded potential donors dying from neoplasms (other than brain tumors), septicemia, and known renal diseases. When in doubt, we have adopted the policy of surgical exposure and examination of the kidneys in the operating room, after permission to use them has been obtained from the next of kin.

TABLE 1
Primary Diseases of Cadaver Donors of Kidneys*

Disease	Donor, number
Coronary heart disease	32
Brain hemorrhage or tumor	26
Valvular heart disease	20
Aortic aneurysm	3
Chronic respiratory failure	2
Acute respiratory failure	1
Malignant lesion	1
Renal artery stenosis	1
Total	86

*Both kidneys were transplanted from 31 cadaver donors; seven kidneys were obtained from hospitals other than Cleveland Clinic Hospital.

The majority of cadaver donors have had a sudden death that occurred in the operating room, the emergency room, or in the intensive care unit (Table 1). Cadaver kidneys have also been obtained from cooperating hospitals in Cleveland and in nearby communities. The technic of obtaining and preparing the cadaver kidneys for transplantation has been presented in a previous publication.[4]

Legality & Public Education

There is a great need to make more cadaver kidneys available for transplantation. Recently the Ohio Legislature enacted a bill that authorizes a living person or the survivors of a deceased person to make a gift of the body or parts thereof after death. Since the "warm" ischemia time (time from the death of the donor to the time when the kidney can be perfused and cooled to 4C) must be less than one hour, speed is essential in the salvaging of cadaver kidneys. Education of the lay public and practicing physicians in regard to the needs of and potential use of cadaver kidney transplantation is essential for continued progress in this field.

In many instances it is obvious at the time of donor nephrectomy that the kidney is nonviable or anatomically unsuitable for transplantation. Our criteria for selecting cadaver kidneys for transplantation have included: consideration of the type of death (sudden or after prolonged illness), the warm ischemia time, the gross appearance of the kidney, and the ease with which the kidney can be perfused. Histochemical technics for assessing viability are currently being studied, and the measurement of the activity of respiratory enzymes in the nephron looks most promising. The results of this determination are available within 30 to 40 minutes after death, and they appear to be a sensitive indicator of the viability of the nephron.

Transplantation

The surgical technics used in renal transplantation have been reported in detail for both living and cadaver kidneys[5] and will not be discussed in this report.

Immunosuppressive Therapy

Azathioprine* in the dosage of from 2 to 4 mg per kilogram of body weight is given immediately postoperatively to each recipient. Later this dosage is tapered to a maintenance dosage that has ranged from 25 to 250 mg per day, depending on the patient's leukocyte count and the presence or absence of manifestations of rejection of the transplanted kidney.

In addition to azathioprine, we have usually administered from 100 to 150 mg of prednisone daily, gradually tapering this dosage when rejection becomes less of a problem. Actinomycin C and local irradiation to the allograft† were utilized in some patients in whom control of rejection was a problem. Recently we have produced antilymphocytic globulin in horses, as described by Iwasaki and associates.[6] A modification of their method of separation of the globulin fraction has enabled us to obtain a much purer immunoglobulin. Since this has been available and administered, the patient has had less pain at the site of injection. No major anaphylactoid reactions have been observed in the 30 patients who received antilymphocytic globulin to date. Eighteen patients received antilymphocytic globulin late in the posttransplantation period in an effort to control a rejection episode that could not be reversed with the usual methods. Twelve patients are still alive with functioning kidneys, and one other patient is alive after nephrectomy of the rejected kidney. It appears that antilymphocytic globulin is a useful adjunct for the control of late rejection reactions.

Twelve patients were treated initially with antilymphocytic globulin as part of the immunosuppressive regimen, and although five of them subsequently died, rejection was not a problem. We have now incorporated antilymphocytic globulin, combined with azathioprine and smaller doses of prednisone, into our standard immunosuppressive program for all patients. The use of antilymphocytic globulin has allowed us to reduce the steroid dosage, and it is our hope that many of the complications due to long-term steroid therapy can be avoided.

*Azathioprine (Imuran), provided through the courtesy of Burroughs, Wellcome and Company, (U.S.A.) Inc., Scarsdale Road, Tuckahoe, New York.

†See Test Your Word Score Page 1083.

Clinical Results

One hundred seventeen kidneys from ca-

TABLE 2
Data on Renal Transplants from Cadaver Donors

Year	Transplants, number	Functioning grafts, number*	Percentage of total, %
1963	9	0(2)**	0
1964	22	8(12)**	36
1965	48	12(24)**	25
1966	22	5(6)**	23
1967†	16	11(2)**	69
Total number of transplants	117		
Total number of patients	97	36	38

*Four additional patients were on the dialysis program.

**Numbers in parentheses are the number of allografts that functioned more than six months.

†To October 1, 1967.

TABLE 3
Length of Survival Time and Clinical Status of Patients with Renal Transplants

Clinical status of patient	Number of patients							
	Length of survival time, months							
	0-6	7-12	13-18	19-24	25-30	31-36	37-42	43-48
Excellent	4	0	0	1	1	1	1	1
Good	2	2	2	4	0	1	0	0
Fair	0	1	2	1	3	3	2	1
Poor	1	0	1	1	0	0	0	0
Total	7	3	5	7	4	5	3	2

daver donors have been transplanted into 97 patients. Of these patients, 40 are alive—36 patients with functioning kidneys, and four patients who are again on the intermittent hemodialysis program awaiting a second allograft (Table 2). The length of survival and the clinical conditions of these patients are shown in Table 3. There are 26 patients alive with transplanted kidneys functioning for more than one year, and two patients have just entered their fifth year, each with a functioning renal allograft from a cadaver donor.

Complications and Postoperative Problems

The various causes of failure in our series of cadaver renal transplants are shown in Table 4.

Nonviable Kidney

Early in our series, inexperience in the selection of appropriate cadaver donors led to the transplantation of a number of kidneys already beyond salvage. Postoperative oliguria usually ensued when an allograft from a cadaver kidney was used, because of the prolonged ischemia time. Prolonged oliguria presents a problem in differential diagnosis, and may be due to acute tubular necrosis, rejection, transplantation of a nonviable kidney, ureteral obstruction, or to a problem with the vascular anastomoses. The management of prolonged postoperative oliguria has been discussed in other reports.[1,7]

Sepsis

Infection is a frequent complication that is difficult to differentiate from rejection and equally difficult to treat. It has been the direct cause of failure in three patients and has caused the death of 24. In an attempt to avoid this complication, all patients are kept in reverse isolation during the immediately postoperative period; no drains are used, and the urethral catheter is removed from the bladder in the first 24 to 48 hours unless the patient has gross hematuria that becomes a problem in management.

Urine Leakage

Leaking of urine caused failure early in four patients, and late in one patient. Leakage is an ominous complication and difficult to manage. In general there was a higher incidence of urine leakage in the kidneys from cadaver donors than in those from live donors, and in most cases it was due to rejection of the ureter. Details of the urologic complications have been discussed in another report.[8]

Hemorrhage

Hemostasis is difficult to obtain in some recipients, as the bleeding is a generalized capillary ooze. The intravenous administration of protamine sulfate during the operation, and direct transfusion from a blood donor have been helpful in controlling this type of bleeding.

Vascular Disease

Venous thrombosis occurred in two patients. In one of these the previous use of cannulas in the external iliac vein, for hemodialysis, had resulted in a thrombus, which was removed at the time of transplantation; but another thrombus formed. Massive thrombosis of both vessels, secondary to rejection, has occurred in three patients, and in each of these there was a mismatch in the ABO blood group.

TABLE 4
Causes of Failure in Renal Transplants

Cause of failure	Early, < 3 months	Late, > 3 months
Rejection	9	8
Nonviable kidney	8	0
Vascular disease	6	0
Hemorrhage	5	0
Urine leakage	4	1
Sepsis	3	0
Agranulocytosis	1	0
Total	36	9

TABLE 5
Causes of Death after Renal Transplantation

Cause of death	Early, < 3 months	Late, > 3 months
Sepsis	13	11
Uremia	6	5
Cerebrovascular accident	4	1
Pneumonia	2	6
Gastrointestinal hemorrhage	2	0
Necrosis of bowel	1	0
Myocardial infarct	0	1
Hepatitis	0	2
Pulmonary embolus	0	1
Not known	1	0
Total	29	27

In one other patient the internal iliac artery thrombosed at the site of an endarterectomy performed to establish improved blood flow at the time of transplantation.

Rejection

Rejection reactions were a major cause of failure and accounted for the loss of nine transplanted kidneys in the first three months postoperatively, and of an additional eight homografts later in the postoperative period. Early recognition and aggressive immunosuppressive* therapy are the key to the management of rejection crises.

Agranulocytosis

Drug intoxication produced agranulocytosis in one patient and caused not only failure of the function of the transplanted kidney but the ultimate death of the patient.

Death

There have been 56 deaths among the 97 patients who received renal allografts from cadaver donors. The causes of death are listed in Table 5.

Summary and Conclusion

Between January 1, 1963, and October 1, 1967, 117 kidneys obtained from cadaver donors were transplanted in 97 patients. The one-year survival rate for these patients is 48 percent, and the overall survival rate is 38 percent.

All recipients initially were in terminal renal failure and were maintained with intermittent hemodialysis before renal transplantation. Bilateral nephrectomy was performed on all recipients, and randomized patients also underwent splenectomy and/or thymectomy. Immunosuppression was accomplished with azathioprine and prednisone, although recently, antilymphocytic globulin has been used, permitting a greatly reduced dosage of prednisone.

Numerous postoperative complications have been associated with renal transplantation, and on 45 occasions the transplanted kidney has failed. In 17 patients a second renal transplant was performed, and in one patient a third, though unsuccessful, attempt was made.

Today, renal transplantation, along with intermittent hemodialysis, must be considered as therapy for the patient with terminal renal failure. Better results in the future will depend on the development of improved tissue-typing technics, on improvement in methods of preserving and storing kidneys for transplantation, on increased availability of donors, and on continued improvement in methods of immunosuppression.

*See Test Your Word Score Page 1083.

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Senescence begins
And middle age ends
The day your descendants
Outnumber your friends.—Ogden Nash

Shakespeare: Medicine

Psychological Disorders

When we meet King Lear he is already old, tired, and doubtless somewhat senile, as manifested by his petulance and rashness. Under Shakespeare's powerfully evocative pen we watch Lear's personality undergo further deterioration—to the point of mental alienation.

Shame and remorse over his own monstrous error in assessing the relative devotion of his three daughters and his subsequent inability to grasp the enormity of Fate's retribution drive him to madness.

Turned adrift by his two elder daughters Lear and his faithful fool wander a whole night on the hostile heath in a raging storm—for daylight to reveal him physically exhausted and mentally aberrant, a state wherein his youngest daughter and his doctor find him: a grotesque figure, raving and "adorned" with weeds—yet retaining shreds of that majesty that characterize him as a king.

Cordelia: Alack, 'tis he! Why, he was met even now
As mad as the vex'd sea, singing aloud,
Crown'd with rank fumiter and furrow-weeds,
With hardocks, hemlock, nettles, cuckoo-flowers,
Darnel, and all the idle weeds that grow
In our sustaining corn.
What can man's wisdom
In the restoring his bereaved sense?

Doctor: There is means, madam.
Our foster-nurse of nature is repose,
The which he lacks; that to provoke in him,
Are many simples operative, whose power
Will close the eye of anguish.

Then later:

Cordelia: How does the King?

Doctor: Madam, sleeps still.

Cordelia: Oh you kind gods,
Cure this great breach in his abus'd nature!

Doctor: So please your Majesty
That we may wake the King? He hath slept long.
Be by, good madam, when we do awake him;
I doubt not of his temperance.

Cordelia: Very well.

Doctor: Please you, draw near.—Louder the music there!

Cordelia: He wakes; speak to him.

Doctor: Madam, do you; 'tis fittest.
He's scarce awake; let him alone a while.

Lear: I am a very foolish fond old man,
Fourscore and upward, not an hour more nor less;
And, to deal plainly,
I fear I am not in my perfect mind.

Doctor: Be comforted, good madam; the great rage,
You see, is killed in him.

Note that the therapy Lear's good doctor used consisted of narcotics for sleep, stimulating music, a beloved daughter's voice, and peace.

So, Cicero Said It

While the sick man has life there is hope.—Cicero

Drug Treatment of Essential Hypertension

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CONTROL OF HIGH BLOOD pressure with antihypertensive drugs prevents many of the complications of hypertensive vascular disease, and increases the length of survival of patients with moderate-to-severe hypertension.[1-4] Control is best achieved when blood pressure is reduced to levels as nearly normal as can be tolerated by the patient. The drug regimen must be well tolerated by the patient, because, except in unusual circumstances, it must be continued for a lifetime. Antihypertensive therapy is strictly palliative, not curative. Despite our incomplete understanding of the mechanisms of hypertension, the great advances in pharmacology of antihypertensive agents permit adequate control of blood pressure in most patients, without objectionable alterations in diet or physical activity, and with a minimum of adverse effects. This type of control requires a thorough knowledge of the drugs available, including their adverse effects and potential toxicity. This report outlines a practical approach to the drug therapy of patients with essential hypertension. The parenteral administration of antihypertensive drugs for hypertensive emergencies will not be discussed here.

Pretreatment Evaluation

Each hypertensive patient deserves a complete and thorough evaluation, preferably before therapy is initiated, unless the hypertension is so severe that delay in administering antipressor drugs would be hazardous. Adequate pretreatment evaluation is designed to answer four questions.

Does the Patient Have Sustained Diastolic Hypertension?

The term "diastolic hypertension" means persistent elevation of the diastolic blood pressure to 100 mm Hg or higher. Random determinations of blood pressure in the physician's office can be misleading. Indeed, if blood

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pressure is labile, repeated determinations over an extended period may be necessary to confirm the existence of diastolic hypertension.

Is the Cause of Hypertension Remediable?

The majority of patients with hypertension suffer from primary or essential hypertension, and a family history of elevated blood pressure may provide a key to diagnosis. In a small group of patients, hypertension may be ascribed to a surgically curable problem: coarctation of the aorta, pheochromocytoma, primary aldosteronism, Cushing's syndrome, unilateral atrophic pyelonephritis or renal artery stenosis. Although less than 10 percent of all hypertensive patients have a surgically curable basis of hypertension, they should be thoroughly tested, since a cure of hypertension is preferable to lifelong medical therapy.

What Is the Patient's General Medical Condition?

The presence of an unrelated, incapacitating illness, or advanced malignant disease, may temper the physician's decision of whether to treat or not to treat the hypertension. The physician may decide against making an intensive search for a remediable lesion, or embarking upon a long, tedious, and expensive program of medical treatment if the patient has an unrelated illness that is a greater threat than hypertension is to his longevity.

How Severe Are the Associated Arteriolar Disease and Atherosclerotic Complications?

The degree of involvement of the so-called target organs—brain, heart and kidneys—is important in the selection of patients for therapy, and in the determination of the level to which blood pressure should be lowered. Atherosclerotic involvement of the target organs, along with retinal arteriolar changes, helps to formulate individual prognoses.

Choice of Drugs

Despite the array of trade names attached to various antihypertensive drugs, singly or in combination, there are only three classes of drugs that warrant discussion: oral diuretics, hydralazine*, and drugs that inhibit the sympathetic nervous system. Of the latter group of compounds, only guanethidine and methyldopa are used extensively in our practice.

Oral Diuretics (Table I)

Chlorothiazide and its many benzothiadiazine derivatives, along with chlorthalidone and quinethazone, have largely replaced Rauwolfia as the 'cornerstone' of antihypertensive therapy. The benzothiadiazine derivatives produce a transient diuresis and negative sodium balance, with a resultant reduction in plasma volume and cardiac output.[5,6] Although decrease in plasma volume may initially reduce the blood pressure, continued administration of these compounds is associated with restoration of the sodium balance, plasma volume, and cardiac output, but not the high blood pressure. The mechanism of chronic maintained antipressor effect remains unclear, although a direct effect upon peripheral arteriolar resistance has been postulated.[7] When orally administered in the suggested doses, all the oral diuretics are comparable in their antihypertensive properties and potential toxicity. In the treatment of severe or malignant hypertension, they provide valuable adjuncts to therapy, as they augment the antipressor effects of ganglion-blocking or sympatholytic* drugs. This permits better control of hypertension with smaller doses of the more potent agents. To a lesser degree they also augment the antipressor response to Rauwolfia compounds and to hydralazine. Oral diuretics should be prescribed with caution for patients with impaired renal function or with gout, since they tend to increase the blood concentrations of urea and uric acid in susceptible patients. Simultaneous administration of probenacid (Benemid) or allopurinol (Zyloprim) will usually prevent the hyperuricemia induced by administration of these drugs, and will make it possible to employ those agents in patients who have gout. Other adverse effects of chlorthalidone, quinethazone, and the benzothiadizine derivatives include hypokalemia, gastrointestinal irritation, weakness, dry mouth, impairment of glucose tolerance, pancreatitis, skin rash or photosensitivity, and, rarely, blood dyscrasias.

Spironolactone and triamterene do not produce potassium depletion, yet they have not achieved the popularity of the kaliuretic drugs.

*See Test Your Word Score Page 1083.

Spironolactone has a modest antihypertensive effect, but it is expensive and must be administered four times daily. Triamterene is a weak diuretic and has little, if any, antipressor action. Either spironalactone or triamterene will minimize or eliminate the hypokalemia induced by therapy with the benzothiadiazine derivatives, chlorthalidone, or quinethazone.

Usually, the hypokalemia induced by these agents is not serious enough to require potassium supplementation or adjuvant therapy with spironolactone or triamterene unless the patient is also receiving digitalis. When potassium supplementation becomes necessary, we prefer to administer it separately in liquid or effervescent-tablet form. Although many of the oral diuretics are available in a combination form containing supplemental potassium, the available potassium rarely is adequate for repletion, and the enteric-coated tablets of this type have been associated with ulcerations of the small intestine.[8]

Ethacrynic acid (Edecrin), a compound chemically unrelated to other oral diuretics, has an antipressor effect comparable to the benzothiadiazine derivatives. A new compound, Furosemide (Lasix), will require more study to prove its efficacy as an antihypertensive drug. Both of these last-mentioned agents are potent diuretics.

Hydralazine (Apresoline)

Hydralazine decreases total peripheral resistance and increases the cardiac stroke volume and heart rate. The resultant reduction in diastolic blood pressure may be greater than the reduction in systolic pressure, and the redistribution of blood flow favors the splanchnic and renal circulations.[9,10] Hydralazine when properly used is a safe and effective antipressor agent. Because of the high incidence of adverse effects associated with its administration, it should not be used as the sole antipressor agent. The adverse effects include headache, palpitations, tachycardia, flushing, and occasionally nausea and vomiting. More serious complications include exacerbation of coronary insufficiency, fluid retention, fever or toxic psychosis. These adverse effects can be largely avoided if the patient is pretreated for several days or weeks with another antipressor agent. A late toxic reaction characterized by a 'collagen-like' syndrome resembling lupus erythematosus rarely occurs if the total dosage of hydralazine does not exceed 300 mg per day.

TABLE 1

Oral Diuretic Agents Used in the Management of Essential Hypertension

Drugs	Trade name	Size of tablet, mg*	Usual daily dose, mg*
Benzothiadiazine derivates			
Chlorothiazide	Diuril	250 or 500	1000-1500**
Hydrochlorothiazide	Hydrodiuril	25 or 50	100-150**
	Esidrix Oretic	25 or 50	
Hydroflumethiazide	Saluron	50	100-150**
Bendroflumethiazide	Naturetin	2.5 or 5	10-15
Trichlormethiazide	Naqua	2 or 4	8-16
	Methahydrin	2 or 4	
Methyclothiazide	Enduron	2.5 or 5.0	10-15
Benzthiazide	Exna	50	100-150**
Polythiazide	Renese	2 or 4	4-12
Cyclothiazide	Anhydron	2.0	2-4
Phthalimidine derivative			
Chlorthalidone	Hygroton	50 or 100	50-100
Quinazoline derivative			
Quinethazone	Hydromox	50	100-150**
Aldosterone antagonist			
Spironolactone	Aldactone-A	25	100-400†

*Given once daily unless otherwise indicated.

**Usually divided and given twice daily.

†Usually divided and given four times daily.

Sympathetic Nervous System Inhibiting Drugs (Table 2)

The compounds that block the sympathetic nervous system act by preventing release, by competitive inhibition, by acting as "false transmitters" or by depleting body stores of catecholamines. Of this group of agents, only Rauwolfia derivatives, guanethidine, and methyldopa are extensively used today.

Rauwolfia alkaloids presumably act by depleting tissues of their catecholamine content, yet do not produce clinical orthostatic hypotension from the doses used. The alkaloids of Rauwolfia are not potent antipressor agents and frequently produce symptomatic adverse effects. Rauwolfia, to be used orally, has been largely replaced by diuretic compounds, since they produce fewer adverse effects and have proved more potent than Rauwolfia in enhancing the responses to other antipressor agents. Objectionable effects include nasal congestion, myalgias, edema, laxation, and gastric hyperacidity. Psychic effects may occur, such as lassitude or disturbing nightmares. A serious psychic reaction is the development of a true depression that may be so severe as to require a psychiatrist's care, but so occult as to escape detection. Depression does not usually occur if the dosage of various Rauwolfia preparations does not exceed the equivalent of 0.25 mg of reserpine daily.

Ganglion-blocking drugs competitively inhibit the action of acetylcholine, the chemical mediator of transmission of nerve impulses at all autonomic ganglions—parasympathetic and sympathetic. Sympathetic inhibition results in reduced arteriolar vasoconstriction, decreased venomotor tone, and increased venous pooling of blood in peripheral vascular beds. Venous return is impaired in the upright position, cardiac output decreases, and orthostatic hypotension, weakness, and syncope occur. The ganglion-blocking agents in common use today are pentolinium and mecamylamine, and doses of either agent are divided and given four times daily. Their greatest disadvantage is the inhibition of the parasympathetic nervous system, resulting in unpleasant or intolerable

TABLE 2

Antihypertensive Drugs That Depress the Sympathetic Nervous System

Drugs	Trade name	Size of tablet, mg	Usual daily dose, mg*
Rauwolfia derivatives			
Reserpine (single alkaloid)	Serpasil Sandril	0.1 0.25	0.1 -0.25
Deserpidine (single alkaloid)	Reserpoid Harmonyl	0.1 0.25	0.2 -0.5
Rescinnamine (single alkaloid)	Moderil	0.25	0.25-1.0
Syrosingopine (synthetic analog)	Singoserp	1.0	0.5 -1.0
Whole root	Raudixin	50 100	100-300
Alseroxylon fraction	Rauwiloid	2	2-4
Ganglion-blocking agents			
Pentolinium bitartrate	Ansolysen	20 40 100	40-400** or more
Mecamylamine hydrochloride	Inversine	2.5 10.0	10-100** or more
Selective sympathetic inhibitors			
Guanethidine sulfate	Ismelin	10 25	10-125 or more
Methyldopa	Aldomet	250	500-2000**
Pargyline hydrochloride	Eutonyl	10 25	10-100 or more

*Given once daily unless otherwise indicated.
**Usually divided and given 3 or 4 times daily.

effects that include blurred vision, dry mouth, constipation, urinary retention, and impotence. The oral diuretics potentiate the effects of ganglion-blocking drugs and may allow blood pressure control with smaller doses. Nevertheless, these agents have all but disappeared from clinical practice since the development of drugs that selectively inhibit the sympathetic nervous system, thus avoiding the effects of parasympathetic blockade.

Guanethidine sulfate (Ismelin) specifically blocks the sympathetic nervous system by inhibiting release of norepinephrine from postganglionic nerve endings.[11] It also depletes tissue stores of catecholamines. In contrast to ganglion-blocking drugs, guanethidine is long-acting, its effect lasting from five to seven days, and tolerance to it does not occur. Like ganglion-blocking agents, it reduces blood pressure more in the vertical than in the horizontal position. Guanethidine has almost eliminated the need for ganglion-blocking drugs, as its antipressor effect is as potent; yet it does not induce the troublesome parasympathetic effects. Because of its long duration of action, guanethidine can be administered as a single daily dose, preferably at the same time each day. The principal adverse effects are orthostatic hypotension, exertional weakness, bradycardia, diarrhea, and impotence or failure of ejaculation. Anticholinergic* drugs will help to control troublesome diarrhea. Potentiation of the antipressor effect of guanethidine by simultaneous administration of oral diuretics will usually permit significant reduction in the dosage requirements for guanethidine.

Methyldopa (Aldomet) inhibits decarboxylase, depletes tissue stores of norepinephrine, and acts as a 'false transmitter' at the sympathetic neuroeffector junction.[12] Alpha-methyl norepinephrine, a metabolite of methyldopa, displaces norepinephrine at the storage sites, and produces a weak pressor response when released by sympathetic stimulation. The antipressor potency of methyldopa is similar in magnitude to Rauwolfia compounds or to oral diuretics. When administered in combination with a diuretic, the antipressor effect exceeds that of combination therapy with a diuretic and either Rauwolfia or hydralazine, and the effect approaches that of guanethidine. Treatment with methyldopa alone or in combination with a diuretic is less likely to result in orthostatic hypotension than is treatment with a ganglion-blocking drug, guanethidine, or pargyline. For this reason, methyldopa is safer than these other drugs in the management of hypertension associated with cerebrovascular or coronary insufficiency. Patients with renal failure demonstrate unusual sensitivity to the antipressor effect of methyldopa, and in these patients it should be used without a diuretic, since renal failure is a contraindication to chronic therapy with diuretics. Adverse effects include mild drowsiness, dry mouth, fever, nasal congestion, depression, abnormal liver-function tests (with or without jaundice), impotence, or fluid retention. Approximately 15 percent of patients receiving methyldopa demonstrate a positive Coombs' test which rarely is associated with hemolytic anemia.

Pargyline hydrochloride (Eutonyl) is a nonhydrazine monamine oxidase inhibitor whose antipressor potency approximates that of guanethidine.[13,14] Its effect is prolonged and cumulative; it is prone to produce orthostatic hypotension, and adjustments in dosage must be undertaken with extreme care. The response to pargyline is enhanced by concomitant treatment with an oral diuretic. Ingestion of foods and beverages containing large amounts of tyramine (certain types of cheese, and beer and wine) may precipitate a dangerous hypertensive crisis in patients taking pargyline. Methyldopa, guanethidine, antihistaminics, sympathomimetic* drugs and other monamine oxidase inhibitors should not be given to patients receiving pargyline. Other troublesome effects include nausea, vomiting, diarrhea, insomnia, impotence or failure of ejaculation, or both. Because of the many drug and food incompatibilities, and because the antipressor effect is not superior to that of guanethidine, pargyline is seldom used.

Therapeutic Regimen in Uncomplicated Hypertension

The key to successful management of hypertension rests with individualization of the therapeutic regimen. The selection of drugs must be influenced by the presence or absence of cardiac, cerebral, or renal complications, by the pretreatment level of the diastolic blood pressure, and by the patient's acceptance of

*See Test Your Word Score page 1083.

the recommended medication. *We do not usually recommend antipressor drugs for patients with labile hypertension in whom the diastolic pressure is not persistently elevated.* Although sustained diastolic hypertension may eventually develop in many of these patients, there is no good evidence that medical treatment will alter this natural course of events. Patients with systolic hypertension (blood pressure higher than 220 mm Hg) may benefit from an oral diuretic. So long as the diastolic blood pressure does not exceed 100 mm Hg and the systolic pressure does not exceed 220 mm Hg, treatment is probably not necessary unless heart failure is present.

Mild-to-Moderate Uncomplicated

Mild-to-moderate uncomplicated hypertension exists when the diastolic blood pressure ranges from 100 to 120 mm Hg in the absence of cardiovascular, renal, or central nervous system dysfunction. Treatment should be deliberate, preferably with the administration of one drug at a time, allowing time for the effect of each agent to be evaluated before administration of another drug is initiated (Table 3). We prefer to initiate treatment with an oral diuretic, which will control the diastolic blood pressure in 40 percent of patients in this category. Methyldopa can be added after from three to six weeks, with gradual increases in dosage to as much as 0.5 g four times daily, if necessary to keep diastolic blood pressure below 100 mm Hg. If step C (Table 3) becomes necessary, administration of guanethidine may be started in a dose of from 10 to 12.5 mg once daily. The dosage may be increased by this amount every two or three weeks, until adequate control of blood pressure is achieved or until adverse effects become intolerable. Hydralazine may be used as an adjuvant agent. It may be worthwhile to add hydralazine in increasing doses to as much as 75 mg four times daily. If no appreciable lowering effect on the blood pressure has been obtained, or if intolerable side effects occur, treatment with hydralazine should be discontinued before proceeding to step C (Table 3).

Severe Uncomplicated

Uncomplicated severe hypertension exists when the diastolic pressure is consistently higher than 120 mm Hg, or when retinal hemorrhage, exudate, or papilledema has occurred. It is now imperative to bring the blood pressure under control quickly, even though cardiovascular or renal complications have not yet developed. The treatment timetable should be expanded with increments in dosage and addition of new drugs being made at more frequent intervals than recommended for the mildly or moderately hypertensive patients. Therapy is initiated with an oral diuretic in optimal dosage, and guanethidine from 10 to 25 mg once daily (Table 3). The dosage of guanethidine should be increased by 10 or 25 mg every three or four days until hypertension is controlled or intolerable effects occur. Treatment is best started in the hospital, but if this is not possible it may be guided by both supine and standing blood pressures obtained two or three times daily at home. When hypertension is not controlled satisfactorily without intolerable effects, we proceed to step B (Table 3) with the addition of methyldopa in doses to as much as 0.5 g four times daily. When guanethidine is ineffective, or when it produces intolerable effects, a ganglion-blocking drug or pargyline may be substituted in combination with the oral diuretic. Methyldopa may be used in combination with a ganglion-blocking drug, but it should not be used concomitantly with pargyline.

Management of Complicated Hypertension

In managing hypertension that is complicated by impairment of cerebral, cardiac, or renal function, special precautions are indicated.

TABLE 3
Outline for Construction of Therapeutic Regimen

Steps in construction of program	Drugs	
	Preferred	Alternate
Mild-to-moderate, uncomplicated hypertension		
Step A	Oral diuretic	Rauwolfia
Step B	Methyldopa	Hydralazine
Step C	Guanethidine	
Severe, uncomplicated hypertension		
Step A	Oral diuretic plus Guanethidine	Oral diuretic plus Ganglion-blocking drug or Pargyline
Step B	Methyldopa	

Congestive Heart Failure

Left ventricular failure in the absence of coronary artery insufficiency is best managed by combination therapy with an oral diuretic and either methyldopa or guanethidine. Sometimes three drugs may be used in combination. Digitalis and dietary salt restriction are also required. Hydralazine may increase cardiac output and cardiac work and is not recommended for hypertensive patients with congestive heart failure.

Coronary and Cerebral Artery Insufficiency

Antipressor therapy should be withheld for from four to six weeks after acute myocardial or cerebral infarction unless hypertension is severe. Thereafter, treatment is instituted as outlined previously. Ismelin, ganglion-blocking drugs, and pargyline must be used with extreme caution, because of their tendency to produce orthostatic hypotension and the threat of increasing vascular insufficiency. Hydralazine should be used with extra caution for patients who have symptomatic coronary disease, because the drug sometimes aggravates coronary artery insufficiency. If hypertension cannot be controlled by an oral diuretic in combination with methyldopa, guanethidine may be added cautiously in small doses.

Renal Failure

Methyldopa and hydralazine are particularly useful in managing hypertension in the presence of renal failure, because they lessen the risk of orthostatic hypotension and consequent compromise in renal blood flow. Oral diuretics should be omitted when values for blood urea exceed 100 mg per 100 ml, unless they are used intermittently for the control of fluid retention. To control severe hypertension in azotemic patients, it may become necessary to use guanethidine in combination with methyldopa or hydralazine. Antipressor therapy should be modified or abandoned if reduction in blood pressure results in further significant elevation in the blood urea concentration. Dietary limitation of protein intake is helpful, and a liberal fluid intake should be encouraged, provided that urinary output is satisfactory.

Summary

A practical approach to the drug treatment of essential hypertension is outlined. The successful control of blood pressure depends upon the skill of the physician in devising a program that will control blood pressure with minimal adverse effects, and upon the reliability of the patient to follow the medical regimen strictly. The control of blood pressure prevents many of the cardiac, cerebral, and renal complications of hypertensive vascular disease, and drug treatment is, therefore, warranted for most patients with sustained diastolic hypertension.

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To lengthen your life, shorten your meals.—Proverb

Nobel Prize Winners In Medicine and Physiology

Robert Barany 1914

For his work on the physiology and pathology of the vestibular apparatus

"As a young otologist I practiced in the clinic of Privy Councillor Professor Politzer in Vienna. Among my patients there were many whose ears I had to flush out. A number of these patients complained of dizziness after the flushing procedure. It naturally occurred to me to examine their eyes, and there I observed marked nystagmus. I made note of this observation. After a while, when I had collected about twenty observations, I compared them and was surprised to find the same observations recorded every time. One of my patients whom I syringed explained to me: 'Doctor, I only get dizzy when the water is not warm enough. When I flush out my ears for myself at home and use warm enough water, I don't get dizzy.' Thereupon I called the attendant and instructed her to give me warmer water for the flushing process. She explained that the water was warm enough. I retorted that if the patient found the water too cold, we had to adjust ourselves to the patient. The next time she put very hot water in the bulb of the syringe. When I syringed the patient, he cried out: 'But Doctor, the water is much too hot; now I'm becoming dizzy again.' Hurriedly I observed the patient's eyes, and noticed that now the nystagmus was exactly opposite in direction to that seen earlier when syringing with water that was too cold. Then in a flash it became clear to me that naturally the temperature of the water was responsible for the nystagmus."

From his studies Barany concluded that the nystagmus was the result of a reflex initiated in the semicircular canals and *ergo; failure* of such syringing to produce nystagmus must indicate disease or destruction of the semicircular canals: a supposition he proceeded to verify by surgery.

Barany's irrigating test is now used extensively to diagnose vestibular disease.*

*With acknowledgments to Theodore Sourkes: Nobel Prize Winners in Medicine and Physiology, 1966.

Plexiglas Hip

In 1948 Khirurgiya (Surgery), a Soviet medical journal, published an extremely interesting article by Professor Dikhno, of Khabarovsk. It describes an operation involving the use of plexiglas.

A 17-year-old youth was unable to walk because his right leg, folded up to his stomach, could not be straightened. Tuberculosis of the hip joint had made a cripple of the boy, and though the disease had subsided, it had done irremediable damage.

Professor Dikhno operated on the youth. The head of the femur, partially destroyed by the disease, had lost its normal shape.

The professor removed the bone adhesions and scars. He also extracted the affected parts of the bones. In place of the former socket the professor fashioned a new one. He then peeled off the affected coating of the head of the femur, causing it to become much thinner. That was sad, since the head was no longer solid enough to support the weight of the trunk. Moreover, it was too small for the newly-scooped socket. But Professor Dikhno enlarged it to the desired size. He put a plexiglas cap on it. The cap was an exact fit.

A month later the operated leg was back to normal. It bent and extended readily. The patient was able to walk.*

*L. Fridland, M.D.: The Achievement of Soviet Medicine, 1961. Edited and translated by W. Horsley Gantt, M.D.

Some Important Colonic and Rectal Polyps

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DORLAND'S MEDICAL DICTIONARY[1] defines a polyp as a "morbid excrescence, or protruding growth from the mucous membrane." In the past, the term classically applied only to a growth on the mucous membrane of the nose, but now it includes such protrusions from a mucous membrane in any part of the body.[2] The colon and, in some instances, the small intestine are hosts to a considerable variety of polyps. Although the adenomatous or papillomatous polyp is the most common, there are other types, each with its distinctive histologic pattern and characteristic biologic behavior. Table I lists a classification that is useful in considering colonic and rectal polyps, and is based upon the clinico-pathologic features of the various polypoid lesions.

In this report the less common but clinically important varieties of polyps are discussed. The common adenomatous or papillomatous polyps have been the subject of a great number of publications, so they will not be considered in detail in this report. In addition, adenomatous polyps are rarely found in childhood unless the patient has familiar polyposis.

Juvenile polyps

Symptoms

Juvenile polyps, as the term implies, occur in childhood and usually are noted as a result of rectal bleeding. Generally the bleeding is red or dark-red and without clots. Blood may be mixed with the feces. Pain is an inconstant feature and, when present, is most frequently of a crampy nature. The polyps may prolapse from the rectum. They may be single or multiple, and for an unaccountable reason boys are more often affected than girls.[2]

Pathology

Juvenile polyps grossly are pedunculated polypoid excrescences, each one comprised of a cylindric stalk attached to a smooth spheroid-

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al tissue mass (Figure 1). In our experience the largest polyp was 2.0 cm in diameter, but polyps up to 3.0 cm have been described.[3] The polyps are deeper red than the normal colonic mucosa, and the cut surface shows a large number of small cysts containing glistening mucoid material. Rarely foci of hemorrhage and ill-defined areas of increased firmness may be present. The polyps histologically are comprised of various-sized colonic glandular structures enmeshed in abundant stroma (Figure 2). Many of the glands are cystically dilated, irregular in contour, and filled with mucus. Frequently the epithelium of the dilated cystic gland is atrophic and notably flattened. An occasional gland may assume a bizarre or complex shape through partial obstruction of a gland orifice. The stroma is distinctive and abundant; it is highly cellular and resembles granulation tissue, being formed of fibroblasts, reticulum fibers, and numerous widespread fine capillaries. In many foci there is an infiltration by lymphocytes and plasma cells, and occasionally there is lymph follicle formation. Histiocytes, neutrophils, and occasionally eosinophils may also be noted in patchy areas. The density of this chronic inflammatory infiltrate is variable and influenced by the ulceration of the surface epithelium that characteristically encompasses the polyps.

The stalks of the juvenile polyps are formed of typical colonic mucosa complete with the muscularis mucosae and a small amount of submucosa. The muscularis mucosae ends abruptly at the zone of attachment of the polyp and does not contribute to the stroma of the polyp. The enveloping single-layered mucus-secreting epithelium of the polyp joins the surface epithelium of the stalk without a transition zone. The stroma closely resembles granulation tissue, or, as Morson[4] interprets it, ". . . it simulates primitive mesenchyme." We share Morson's[4] view that these lesions represent hamartomas of the mucosal connective tissue, though Roth and Helwig[5] have suggested that the juvenile polyp represents a polypoid transformation of a local submucosal inflammatory process. Juvenile polyps do not appear to be predisposed to malignant change.

TABLE I
Classification of Polyps of the Colon and Rectum

- A. Developmental, congenital, familial polyps
  - 1. Juvenile
  - 2. Juvenile polyposis coli
  - 3. Peutz-Jeghers syndrome
  - 4. Familial polyposis
- B. Inflammatory polyps
  - 1. Pseudopolyps (chronic ulcerative colitis)
- C. Neoplastic polyps
  - A. Of colonic mucosa
    - 1. Adenomatous or papillomatous
    - 2. Carcinoid
  - B. Of tissues other than mucosa
    - 1. Lymphoid polyp (benign lymphoma)
    - 2. Lipoma
    - 3. Fibroma and neurofibroma
    - 4. Leiomyoma
    - 5. Hemangioma

Treatment

No carcinomas of the colon or of the rectum arise from such polyps. Only symptomatic ju-

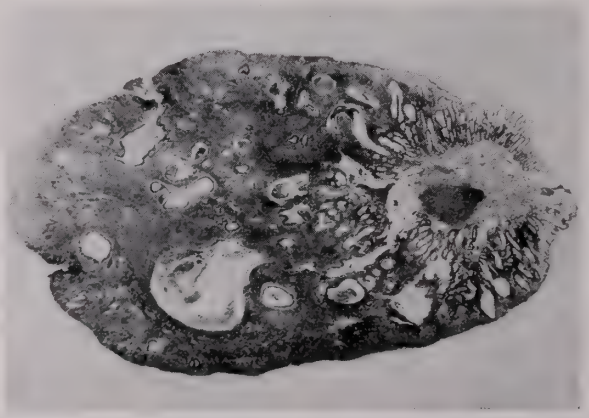


Fig. 1—Juvenile polyp showing cystically dilated colonic glands enmeshed in abundant stroma. Note the smooth outline of the polyp. H + E, ×7.

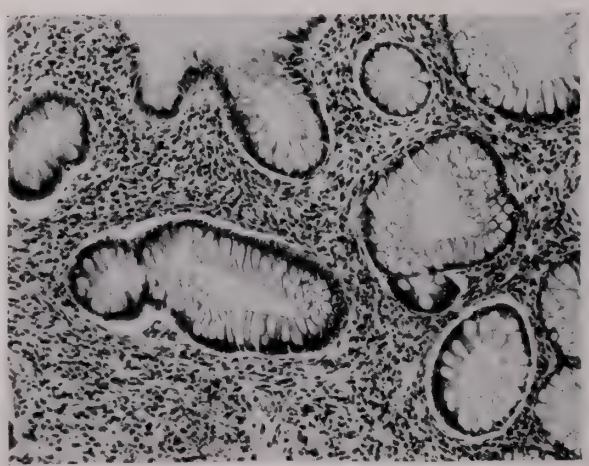


Fig. 2—Juvenile polyp showing the normal character of the epithelium and the granulation tissue-like or mesenchymal appearance of the stroma. H + E, methylene blue, ×135.

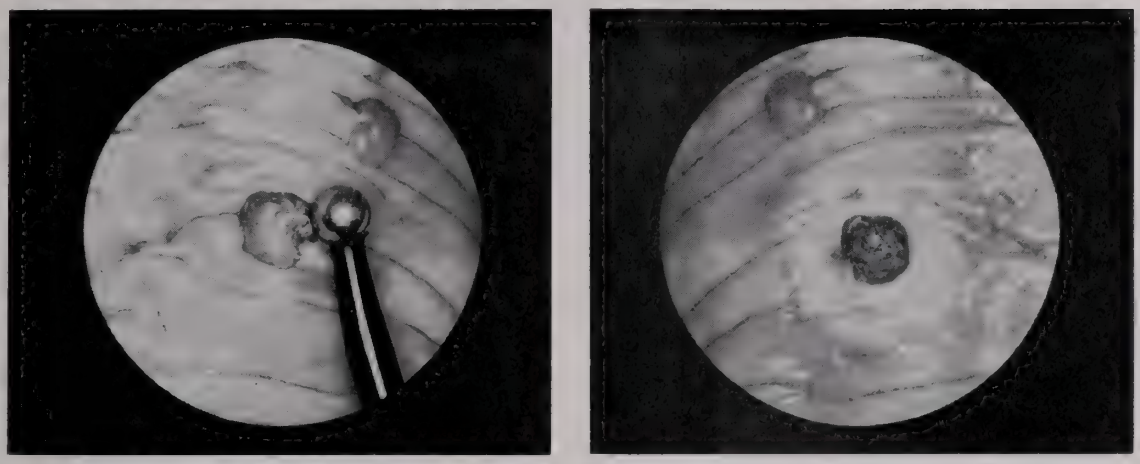


Fig. 3—Electrocoagulation of a polyp. A (left) Electrocoagulation by the electrode has begun. B (right) Electrocoagulation of the polyp has been completed. Note that a margin of adjacent mucosa is also coagulated; this ensures complete destruction of polyp tissue.

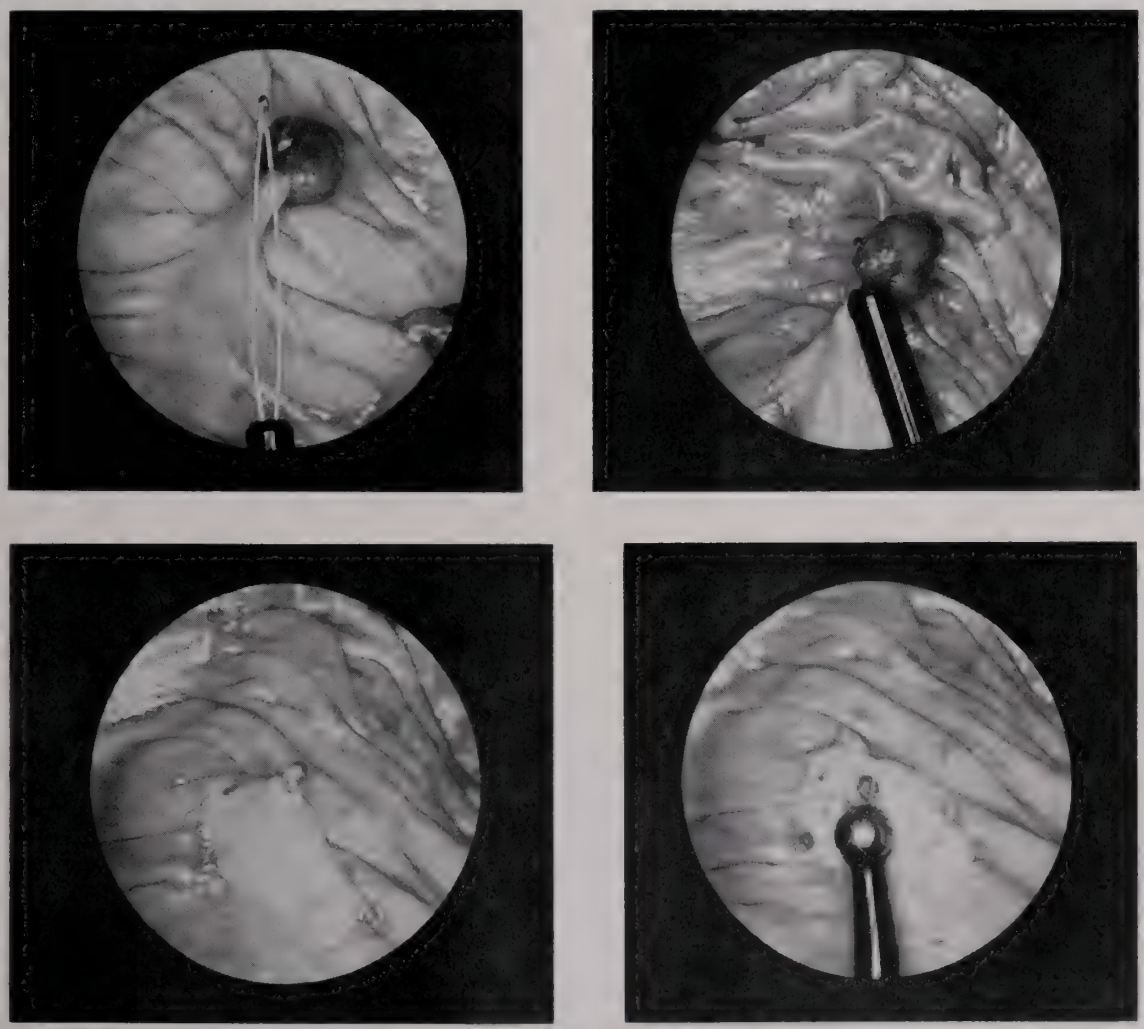


Fig. 4—Snare excision of a polyp. A (top—left) The polyp pedicle is encircled by the snare. B (top—right) The snare is closed around the pedicle, and the blended current is applied. C (bottom—left) The pedicle base remains. Bleeding is absent because coagulation and cutting currents were applied simultaneously. D (bottom—right) The pedicle base and adjacent mucosa have been coagulated.

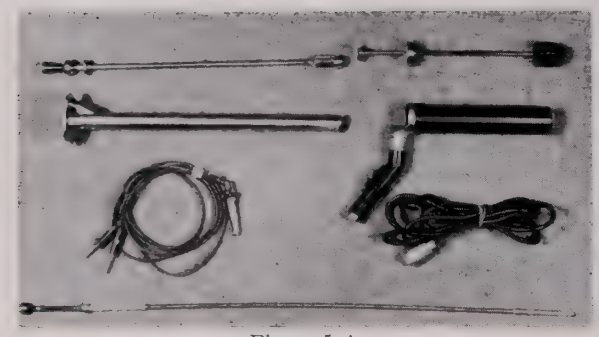


Figure 5-A



Figure 5-B

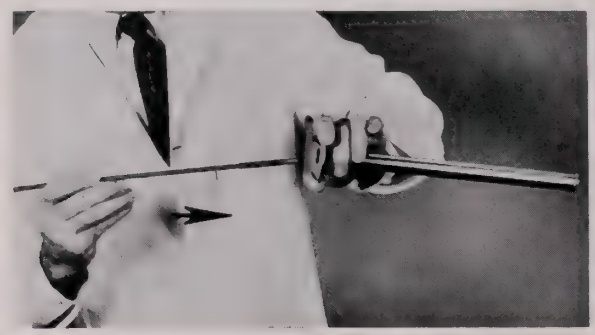


Figure 5-C



Figure 5-D



Figure 5-E

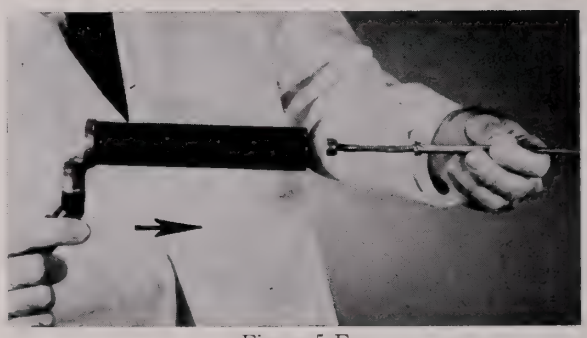


Figure 5-F



Figure 5-G

Fig. 5—Method for bringing a sigmoid polyp into the range of an operating proctoscope. A, The required equipment includes a diagnostic proctosigmoidoscope (upper left), an operating proctoscope (upper right), and a flexible grasping instrument (below). B, The "fingers" of the grasping instrument are shown opened. C, After visualization of the polyp through the diagnostic proctosigmoidoscope, the clinician passes the grasping instrument into the proctosigmoidoscope. D, The polyp has been grasped. E, the proctosigmoidoscope is being withdrawn. F, The operating proctoscope is being passed around the grasping instrument. G, Traction on the grasping instrument has delivered the polyp into the range of the proctoscope for easy removal by snare, ligature, or forceps.

venile polyps need be excised, and then by the most conservative measures possible. Bleeding is the most common indication for removal. It should also be remembered that in many instances juvenile polyps will separate spontaneously from the wall. If completely removed they do not recur.

When there are multiple small juvenile polyps, coagulation suffices (Figure 3A, B). It is well to remove larger polyps, if possible, because of the danger of intussusception or prolapse of the polyp. If the polyp can be seen through the proctosigmoidoscope, it can be removed. If it is in the rectum—especially if on the retroperitoneal wall—it can be removed by snare or forceps without anesthesia (Figure 4 A-D). If it is in the sigmoid, it can be grasped through a diagnostic proctosigmoidoscope and then brought down to the level where it can be removed easily through an operative proctoscope. This should be done with anesthesia (Figures 5 A-G). Occasionally excision must be performed at laparotomy and colotomy (Figures 6 A-J). Asymptomatic colonic polyps, once the diagnosis has been established, need not be removed.

Juvenile Polyposis Coli

Veale and his colleagues[3] have reported a series of 11 cases of multiple juvenile polyps, giving the histopathologic and clinical features, and the family histories. There were eight girls and three boys in the series, a reverse of sex incidence of that noted for isolated juvenile polyps. Polyps were found throughout the colon in seven of the patients, but in four were limited to the rectosigmoid. Of interest is that the ileum was affected in two patients. Subsequent cases have been reported by others.[6]

The histology of the lesions of juvenile polyposis coli was identical to that of juvenile polyps. In some of the cases there was a family history of juvenile polyposis or of cancer or of both types of lesions of the large bowel. Veale and associates[3] postulate that the disease is brought about by the modification of the action of the gene for adenomatous polyposis coli by an allele* received from a normal parent. Isolated cases of the disorder are considered to arise from fresh mutations.

*See Test Your Word Score page 1083.

According to present knowledge and to our own clinical experience, treatment should be conservative, since, as yet, cancers have not been found in this group of patients. Occasionally resection may be required in cases of troublesome bleeding, intussusception or protein loss.

Peutz-Jeghers Syndrome

Mucocutaneous pigmentation and intestinal polyposis together comprise Peutz-Jeghers syndrome.[7,8] The polyps develop both in the large and in the small intestine, and occasionally in the stomach. Gastrointestinal bleeding, abdominal pain, and intussusception of segments of the intestine are the most frequent symptoms. The disorder is familial and is thought to be inherited as a simple mendelian dominant trait.

The intestinal polyps grossly resemble the common colonic papillomatous or adenomatous polyps. They are finely fissured, soft, pink, irregularly spheric, ranging in largest diameter from a few millimeters to approximately 2.5 cm. A slender but well-defined stalk or pedicle is always present. The basic histologic appearance of the polyp in Peutz-Jeghers syndrome is that of an arborizing fibromuscular stroma that appears to originate from a central smooth-muscle mass (Figure 7). This muscle mass appears to arise in the muscularis mucosae of the intestine and is continuous with it. The epithelial component of the syndrome closely resembles the normal mucosa of the gastrointestinal tract, in which the polyp is located, and is comprised of typical intestinal glands enmeshed in a lattice-work of fine fibrous tissue similar to that of the lamina propria of the normal gastrointestinal tract. As in the normal lamina propria, there is an interstitial infiltrate of a few polymorphonuclear leukocytes, plasma cells, and histiocytes. An important feature is the relationship of this mucosa to the supporting fibromuscular stroma; it is identical to the relationship of mucosa to muscularis mucosae. The arborizing fibromuscular stroma is formed principally of smooth muscle in the central portions of the lesion, but as one approaches the more peripheral areas of the polyp, the smooth-muscle components become discontinuous, though in most areas wisps of smooth muscle can be identified. The grandular component of these polyps is formed of typical tubular intes-



Figure 6-A

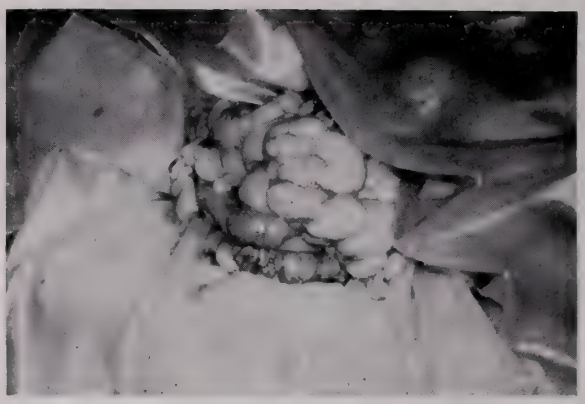


Figure 6-B



Figure 6-C

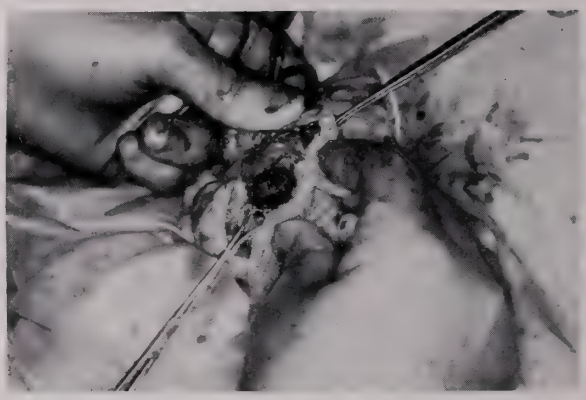


Figure 6-D



Figure 6-E



Figure 6-F

Fig. 6—Method of polyp removal by laparotomy and colotomy. A, A barium-air contrast roentgenogram shows a sigmoid polyp on a pedicle. B, At laparotomy, the sigmoid wall bulges at the location of the polyp. C, A transverse colotomy incision has been made. D, The polyp is being delivered through the colotomy incision. E, The pedicle has been ligated. The polyp is shown wrapped in a sponge saturated with a 40 percent alcohol solution to prevent scattering of viable malignant cells that might be present. F, A suture ligature is being placed distal to the free ligature; this affords reliable ligation without danger of hematoma formation.



Figure 6-G



Figure 6-H



Figure 6-I

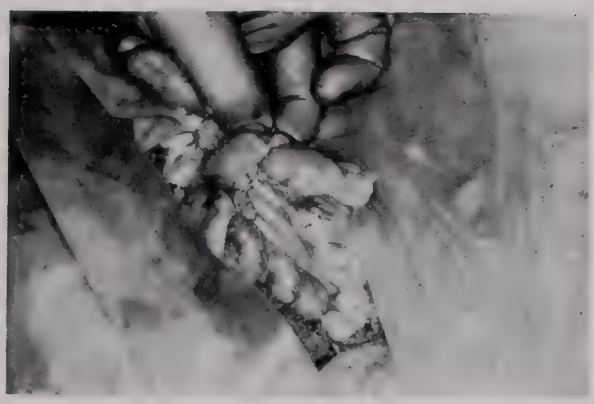


Figure 6-J

Fig. 6—Method of polyp removal by laparotomy and colotomy (Continued) G, The pedicle is being amputated distal to the double ligation. H, Bowel near the colotomy is being examined digitally for other palpable lesions. I, Bowel distant from the colotomy is being inspected by means of colonscopy. J, The colotomy has been closed transversely by two layers of sutures.

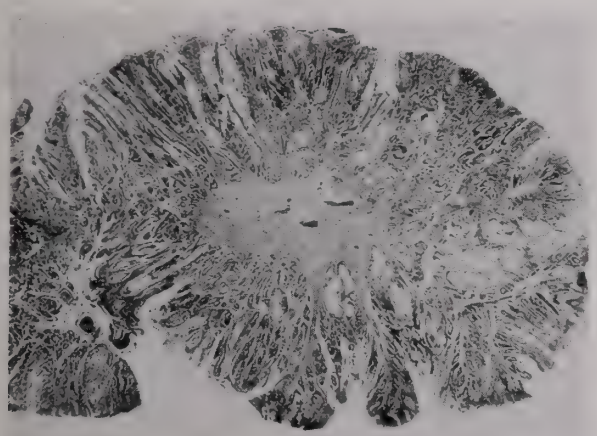


Fig. 7—Typical polyp of Peutz-Jeghers syndrome. The arborizing fibromuscular stroma is clearly apparent. H + E, methylene blue, ×7.

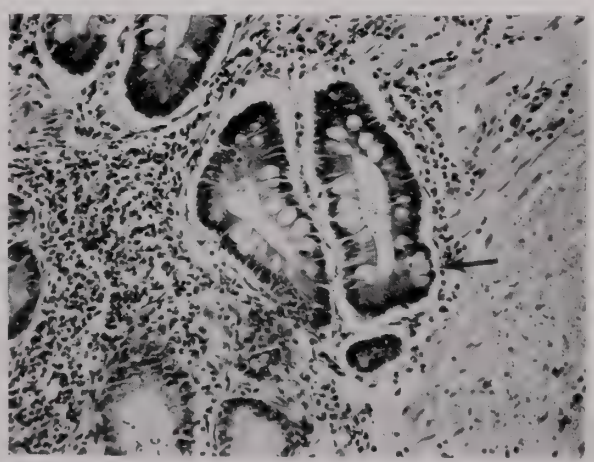


Fig. 8—Paneth's cells (arrow) are readily found in the polyps of the small intestine in Peutz-Jeghers syndrome. H + E, methylene blue, ×200.

tinal glands, some of which may become distorted or cystically dilated because of obstruction of the orifices. In the instance of small intestinal polyps of Peutz-Jeghers syndrome, formations closely resembling crypts of Lieberkühn can be identified, and in the base of these crypts one can frequently find Paneth's cells and argentaffin cells (Figure 8). In the colonic polyps, however, Paneth's cells are not usually found because they are not frequent inhabitants of the colonic mucosa.

Bartholomew and associates[9] have considered these polyps to be hamartomas. This seems a logical concept in view of the microanatomy of the polyps, which appears to be the result of a localized arborizing proliferation in the muscularis mucosae. Histologically the complex fibromuscular core is continuous with the muscularis mucosae of the intestinal tract, and the mucosal covering is essentially normal. Morson[4] suggests that the mucosa is abnormally placed. The presence of Paneth's cells and argentaffin cells would seem to confirm the normalcy of the mucosal covering.

Although Peutz[7] in his original consideration noted "malignant degeneration" of the polyps in three of seven patients, metastasis and death due to malignant disease were not established. The possibility of histologic misinterpretation of glandular structures enmeshed in the fibromuscular stroma as polypoid adenocarcinoma may explain this observation (Figure 9). A documented case of malignant degeneration and metastasis in the Peutz-Jeghers syndrome has been reported by Achord and Proctor.[10] The incidence of such a catastrophe, however, seems so extremely low that the recommendation for surgical treatment should be limited to the relief of obstruction and bleeding.

Comment

The polyps considered above are highly distinctive and different from the common papillomatous or adenomatous polyps in at least several respects. Grossly papillomatous polyps are pedunculated, finely fissured or even finely villous, lacking the smooth external surface of juvenile polyps that are further characterized by punctuating mucous cysts and small patches of ulceration. Polyps in the Peutz-Jeghers syndrome are less distinguishable grossly, but usually are not so finely fissured. The stroma

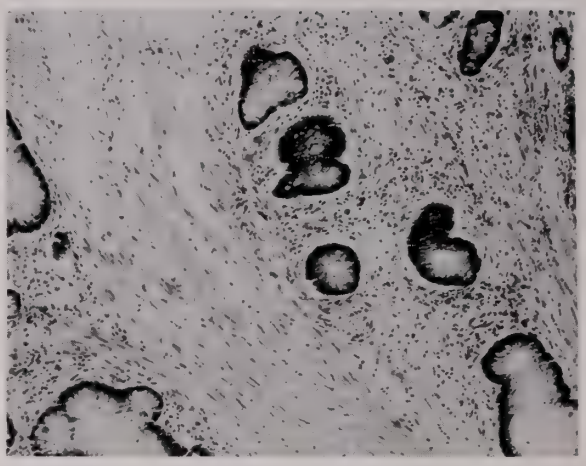


Fig. 9—Polyp of Peutz-Jeghers syndrome, showing normal colonic glands entrapped in the fibromuscular stroma, a feature that may erroneously be interpreted as stromal invasion. H + E, methylene blue, ×100.

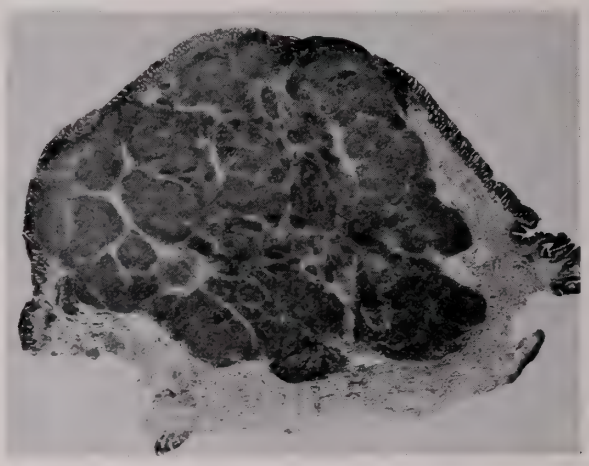


Fig. 10—Lymphoid polyp formed of the typically sharply demarcated lymph follicles. H + E, methylene blue, ×6.

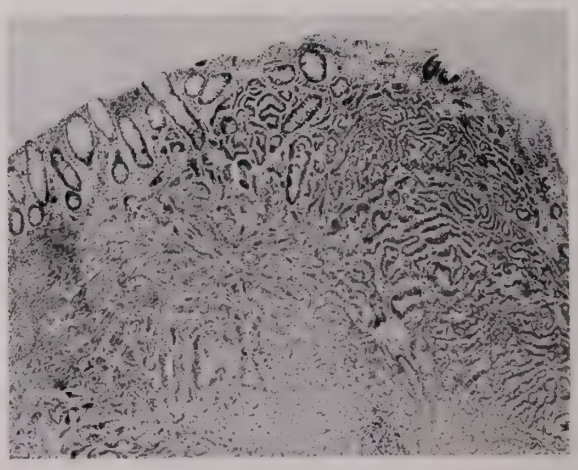


Fig. 11—A polypoid carcinoid showing the uniformity of the argentaffin cells and the invasion of submucosa and muscularis. H + E, methylene blue, ×50.

of adenomatous or papillomatous polyps is fibrous and vascular and is most abundant at the hilum or point of attachment of the polyp stalk, becoming quite inconspicuous at the periphery of the lesion. The mesenchymal appearance of the stroma of juvenile polyps and the smooth muscle component of Peutz-Jeghers polyps are certainly distinctive features. In addition, the epithelium of these polyps demonstrates its neoplastic qualities by such alterations as pseudostratification, hyperchromatism, and increased mitotic activity. In some polyps, foci of carcinoma in situ may be found. These epithelial features have not been observed as yet in juvenile polyps or polyps of Peutz-Jeghers syndrome.

The principles of treatment of patients with juvenile polyps are similar to those of the therapeutic management of patients with Peutz-Jeghers syndrome. Conservative removal of symptom-producing polyps is indicated.

Lymphoid Polyps

These rather uncommon lesions occur usually as round, mound-like polypoid masses in the rectum. They are rarely pedunculated. They are covered by a smoothed-out colonic mucosa. Ulceration, with secondary inflammatory changes, is common. A cross section of one of these lesions reveals a sharply circumscribed, rather homogenous, grayish mass of tissue in the submucosa, which elevates the mucosa. Histologically this polyp may be considered as a colonic tonsil without crypts, for it is formed of well-defined, well-differentiated lymphoid tissue, complete with typical germinal centers (Figure 10). Small numbers of mitoses may be seen within the germinal centers. The lymphocytes about these centers are mature, and miototic figures are not readily found there.

These excrescences are usually found in the rectum, principally in the lower third part. Rectal bleeding, prolapse of the polyps, and pain are the most common presenting symptoms. Cornes, Wallace, and Morson,[11] and Helwig and Major[12] have written about these lesions and have applied the brief term *benign lymphoma* to them. In their experience and in ours, none of these polyps have been associated with systemic lymphoma. However, in the series from St. Mark's Hospital, carcinoma of the rectum was associated in seven of 100 patients.[11] Therapy of these polyps has been conservative, usually limited to simple removal or electrocoagulation.

Carcinoid Tumors

The carcinoid tumor of the rectum is a gritty hard polyp. The original appears to be from the depths of the mucosa, and frequently the bulk of the tumor mass is present in the submucosa, and the lesion is entirely covered by normal colonic mucosa. The cut surface may be yellowish or grayish-white and is usually quite firm. Histologic section reveals rather distinctive uniform hyperchromatic small-to-medium-sized cells arranged in festoons or in a glandular pattern (Figure 11). Mitotic figures are extremely rare. The tumors are locally infiltrative and may invade the muscularis propria—leading the pathologist occasionally to describe them as undifferentiated cancers.

Special-staining reactions may or may not reveal the ability of these tumors to reduce ammoniacal silver salts. This special staining technic is highly useful when the result is positive, but a negative result does not necessarily exclude the diagnosis of carcinoid. The argentaffin granules are thought by some to represent artifacts produced by the chemical fixation, and actually to be serotonin. Morson[4] explains the failure to demonstrate these argentaffin granules by stating that tumors without them have arisen from Kultschitsky's (argentaffin) cells before these elements have achieved the ability to produce granules.

Carcinoids, as the name implies, are potentially malignant lesions. Bates,[13] in an excellent review of the subject, reported that the carcinoid lesions that are less than 1.0 cm in cross diameter are rarely clinically malignant; whereas, of those more than 2.0 cm in greatest diameter, approximately from 75 to 80 percent give rise to metastasis. Of the lesions that are less than 2.0 cm in diameter and which are malignant, most penetrate into the muscularis propria.

Men are slightly more commonly affected than women, and the peak instance for these lesions is the sixth decade for men and the fourth decade for women. In Bates'[13] series, most of the benign lesions were present in the

middle third of the rectum on the anterior wall; whereas most of the malignant lesions were annular and occurred in the lower two thirds of the rectum.

Summary

These four different types of colonic polyps are especially important because they present little chance of lethal malignant disease. They are best managed by local treatment.

Large or annular lesions usually require resection. Carcinoids less than 1.0 cm in diameter should be removed by local excision. The tumor must be removed without cutting into it, for implantation of tumor cells can occur, especially when sutures are required. Electrosurgical methods of excision minimize the possibility of implantation.

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Early Follies

The demarcation between the legitimate physician and the quack was shadowy during the eighteenth century and for some time to come, because of the tenuous basis of the former's theory and practice. Thomas Percival could write with great justification in 1777:

"A list of all the follies which at different times have been established as articles of faith in medicine, would form the severest satire on the healing art. Who can withhold his laughter when he reads of expelling, attracting, and concocting faculties; of energies, sympathies, antipathies, idiosyncrasies, and occult causes; of the body being nothing but salt, sulphur, and mercury; of man being a microcosm, and uniting in his frame the motion of the stars, the nature of the earth, of water, air, all vegetables and minerals, the constellations, and the four winds. Yet ridiculous as these several tenets may appear, they have given rise to sects, have been espoused with warmth, and defended with acrimony."

At that time the "animism" of Stahl, the "aether" of Hoffman, the "solidism" of Cullen, the "iatrochemical' and "iatro-physical" and "Old Vienna" schools were popular in different medical circles, while the less speculative work of Harvey and Sydenham had hard sledding.*

*Bernhard Stern: Society and Medical Progress, 1941.



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Note: Ovulen remains available in the familiar round Compack for those women who may wish to continue to use the traditional 20-day schedule. Be sure to specify Ovulen-21 to assure each new patient of the advantages of the new *Three Weeks On—One Week Off* schedule. She might appreciate your budget-minded authorization for a six-month supply (five Refills).

Indication — For oral contraception.

Contraindications — Thrombophlebitis or a history of thrombophlebitis or pulmonary embolism, liver dysfunction or disease, known or suspected carcinoma of the breasts or genital organs and undiagnosed vaginal bleeding.

Warnings — Discontinue medication pending examination if sudden partial or complete loss of vision, or sudden onset of proptosis, diplopia or migraine occurs. Discontinue if papilledema or retinal vascular lesions occur. Since the safety of Ovulen in pregnancy has not been established, rule out pregnancy before a patient who has missed two consecutive menstrual periods continues the tablets. Consider the possibility of pregnancy at the first missed withdrawal flow if the recommended schedule has not been followed. The active ingredients in oral contraceptives have been identified in the milk of mothers receiving these drugs. The significance of this to the infant has not been determined.

Precautions — The pretreatment physical examination should specifically include the breasts, pelvic organs and a Papanicolaou smear. Endocrine and possibly liver function tests may be affected by Ovulen. Such tests should be repeated two months after stopping the medication if their results were abnormal in a woman taking Ovulen. Pre-existing fibroids may enlarge under the influence of progestin-estrogen preparations. Patients with epilepsy, migraine, asthma, cardiac or renal dysfunction, which conditions might be influenced, require careful observation because Ovulen may cause some degree of fluid retention.

Ovulen should be used with caution in patients with a history of cerebrovascular accident. Nonfunctional causes should be considered if breakthrough bleeding occurs. Adequate diagnostic measures are indicated in women with undiagnosed vaginal bleeding. Carefully observe patients with a history of psychic depression and discontinue the medication if depression recurs to a serious degree. Any possible influence of prolonged Ovulen use on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. Carefully observe diabetic patients during Ovulen use since a decrease in glucose tolerance has occurred in a few such patients. Physicians should be alert to the earliest manifestations of thrombophlebitis and pulmonary embolism since such conditions occasionally occur in patients taking oral contraceptives. Use Ovulen judiciously in young patients in whom bone growth is not complete because of the effects of estrogens on epiphyseal closure. Age is no absolute limiting factor, although Ovulen use may mask the onset of the climacteric. Pathologists should be informed of Ovulen use when relevant specimens are submitted.

Side effects — The following adverse reactions have been observed in varying incidence in patients taking oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea, edema, chloasma or melasma, breast changes (tenderness, enlargement, secretion), change in weight (increase or decrease), changes in cervical erosions and secretions, suppression of lactation when used immediately post partum, cholestatic jaundice, migraine, allergic rash, rise in blood pressure in susceptible individuals and mental depression.

Although the following side effects have been reported in users of oral contraceptives no cause and effect relationship has been established: anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme and nodosum, hemorrhagic eruption and itching. Thrombophlebitis, pulmonary embolism and neuro-ocular lesions have occurred in users of oral contraceptives, although a cause and effect relationship has been neither established nor disproved.

The following laboratory results may be altered by oral contraceptives: Bromsulphalein® and other hepatic function tests—increased; coagulation tests, including prothrombin, Factors VII, VIII, IX and X — increased; thyroid function — increase in protein-bound iodine and butanol extractable protein-bound iodine, and a decrease in T^3 values; metyrapone test and pregnanediol determinations.

Dosage and administration — One tablet of Ovulen-21 daily for 21 consecutive days, beginning five days after the onset of a menstrual flow (the first day of menstruation is counted as day 1), then discontinued for one week. If Ovulen is started later than day 5 after menses begins another method of protection is used until the first seven tablets have been taken. Subsequent 21-day courses are begun on the eighth day after the last tablet was taken in the preceding cycle. This three weeks on — one week off schedule is continued whether or not withdrawal flow has begun, flow has ceased or spotting or breakthrough bleeding has been experienced.

If one tablet is missed it is to be taken as soon as it is remembered and the next tablet at the usual time. If two consecutive tablets are missed the dosage is doubled for the next two days, then the regular schedule is resumed. If three consecutive tablets are missed a new tablet cycle is started on the eighth day after the last tablet was taken. For the best protection in the latter two instances instruct the patient to use another method of contraception until the next seven consecutive tablets have been taken. The possibility of ovulation increases with each successive tablet missed.

Postpartum administration — Non-nursing mothers may begin Ovulen immediately after delivery and nursing mothers after lactation is well established.

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Contraindications: Severe central nervous system depression, comatose states from any cause, hypertensive or hypotensive heart disease of extreme degree.

Warnings: Administer cautiously to patients who have previously exhibited a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) to phenothiazines. Phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides. During pregnancy, administer only when necessary.

Precautions: There have been infrequent reports of leukopenia and/or agranulocytosis and convulsive seizures. In epileptic patients, anticonvulsant medication should also be maintained. Pigmentary retinopathy may be avoided by remaining within the recommended limits of dosage. Administer cautiously to patients participating in activities requiring complete mental alertness (e.g., driving). Orthostatic hypotension is more common in females than in males. Do not use epinephrine in treating drug-induced hypotension. Daily doses in excess of 300 mg. should be used only in severe neuropsychiatric conditions.

Adverse Reactions: *Central Nervous System*—Drowsiness, especially with large doses, early in treatment; infrequently, pseudoparkinsonism and other extrapyramidal symptoms; nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache. *Autonomic Nervous System*—Dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, nasal stuffiness, and pallor. *Endocrine System*—Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema. *Skin*—Dermatitis and skin eruptions of the urticarial type, photosensitivity. *Cardiovascular System*—Changes in the terminal portion of the electrocardiogram have been observed in some patients receiving the phenothiazine tranquilizers, including Mellaril (thioridazine hydrochloride). While there is no evidence at present that these changes are in any way precursors of any significant disturbance of cardiac rhythm, several sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients previously showing electrocardiographic changes. The use of periodic electrocardiograms has been proposed but would appear to be of questionable value as a predictive device. *Other*—A single case described as parotid swelling.

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Editorials

Minnesota Medicine and the Cleveland Clinic

SPECIAL ISSUES of a journal from one institution have, I believe, the chief merit of giving the reader a sample of its flavor. Often quite unconsciously such an issue betrays the collective interests of the staff, and it is the staff that is the core and consciousness of an organization.

Over the past 28 years I have watched and participated in the slow change in character of the Cleveland Clinic. I suspect I entered the institution during the demise of an era—an era characterized by vigorous and highly skillful surgery, a make-do era as regards physical equipment and plant, an era of one-man rule in each bailiwick, an era when research was for second-class citizens, and an era when public funds were anathema. The volume of surgery did not increase proportionately to that of medicine with the passing of time, thanks to increasing use of antimicrobial agents and increasing understanding of the mechanisms of disease. Psychiatry became acceptable and rehabilitation of the physical plant began; leaded glass windows were replaced by sealed-in windows and air conditioning.

But intellectually, the two greatest changes were the hectic growth of research in cardiovascular disease and its application, and the diffusion of responsibility to the younger staff. It has been said somewhat cynically that in big institutions, Peter's principle applies, i.e., each employee tends to rise to his level of incompetence. Thus, in theory, employees are promoted until they reach a position for which they are incompetent, and there they stay. This, of course, is in the main untrue. A broader spectrum of responsibility in the young institutional physician, in my opinion, makes him grow up sooner. The only real loss in diffusion of authority is twofold: (1) some of the discipline of the physician's life in relation to his patients and the institution may vanish, and (2) there is too little concentrated authority for a leader to make sensible exceptions to general rules. This latter trend inevitably makes duplication of people quite as rapid as the Xerox machine makes of reports.

When I look back, I look forward with the greater satisfaction. The younger generation may not be as erudite as we are, but it is amazing how fast they learn so much more than we ever will. I commend the contents of this issue of MINNESOTA MEDICINE to the reader as proof of this contention.

Irvine H. Page, M.D.*
Cleveland, Ohio

*Director Emeritus, Research Division of The Cleveland Clinic Foundation.



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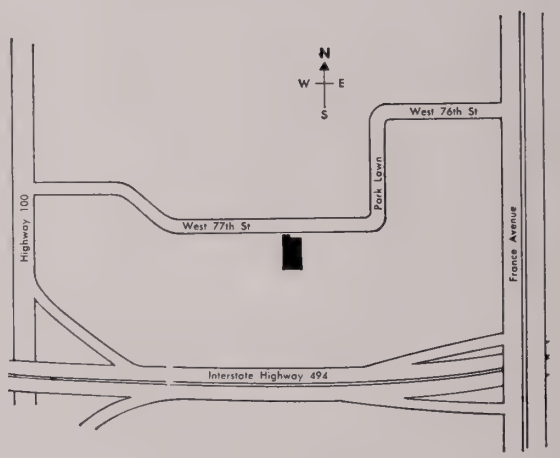
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The Editors of MINNESOTA MEDICINE

WITH THIS issue MINNESOTA MEDICINE is privileged to publish a significant group of papers from the Cleveland Clinic, which ranks among the great private medical institutions in the world providing service unstintingly to all who seek it. As one would expect in this country of medical free enterprise, such a concentration of medical talent in one institution promotes special studies of unusual diseases and treatment not practicable in a smaller institution. The Cleveland Clinic's kidney dialysis and cardiac units represent a contribution to medicine which would be impossible under the intricacies of a bureaucratic system.

The Board of Editors of MINNESOTA MEDICINE thank the Cleveland Clinic for their papers in this issue. We invite this Clinic and other medical organizations, who might wish to present their material to physicians, to publish again in future issues of MINNESOTA MEDICINE.

Problems in Health Care

THE PAST 25 years of my life have been very interesting, albeit strenuous, for they mark a time when I have been acutely conscious of strife about the practice of medicine. Many physicians, especially the younger but not exclusively they, will find it astonishing that the situation that troubles all of us in medicine has existed so long.

When in the 40's a National Health System was proposed in Congress, the annual national expenditure for health was $8 billion. We then pondered what effect this legislation would have on future expenditures for medical care and predicted direly that it might go as high as $15 billion. Almost everyone knows the amount has now risen to $40 to $50 billion, without a National Health System, reflecting the will of the people to put this much of their income into health care.

More recently the Congress decided to inject approximately $5 billion into the health care industry. This action has satisfied some demands but at the same time has created a great deal of dissatisfaction and unrest in a system which, while far from perfect, is quietly doing the work. In many respects our progress has been spectacular. One bit of supporting evidence is that the United States has become the center of the world's interest in medical affairs.

An important development during this 25-year period is that population shifts have upset the distribution of health care to people as they congregated here and dissipated their numbers there. Thus pockets of concentrated need and open spaces of widely dispersed demand were created without any apparent substitute to take the place of the former cozy relationship of a relatively small unit of population with its own physician or "doctor."

Another problem is that of financing health care. Subsidizing the care of the medically indigent requires expenditures locally and nationally that are shocking to contemplate. Paying agencies react by suggesting controls, stricter definitions of eligibility for benefits and arbitrary regulation of the prices paid for units of service. Perhaps we should recognize these actions as evidence of fiscal responsibility to be preferred to the roseate promises of free care. Regulations and guidelines are not perfect and require development. The providers' understanding is needed to make them equitable and just.

Distribution of services is related to such characteristics as numbers, availability, effi-

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ciency, and a quality of effectiveness. Much service demand we know is elective. Looking at the supply end we tend to blame someone for insufficient numbers of health workers. While we must continue our efforts to educate and train more physicians, nurses and allied personnel, we also should acknowledge that there are finite limits to the education system. Consequently more consideration should be given to the efficient use of our available resources. Ordinarily in medicine, crash programs are neither practical nor successful. The evolutionary approach will serve us still if we are alert.

It is often said that health service providers are not readily available at all times. Actually this laudable objective can only be approximated. I do not find it astonishing, when one considers the size of our country, that someone sometime will suffer an emergency unattended. However, the occasion still is so infrequent as to attract front page attention. I do not find it strange that health workers might seek relief from a 168-hour week. As they see their fellow citizens enjoying leisure and recreation, providers should be expected to yearn for some of these same pleasures. It is not a lack of devotion so much as a need for a plan for substitution or replacement. Proper planning will solve many of our difficulties.

There is a lot of work to be done to improve our situation. Unless one wants to be pedantic there is no crisis; but there is no room for complacency, either. We must provide new forms of organization for delivering health services and devise ways to make the financing of health care reasonable. This is our charge. We must keep working at it.

Charles L. Hudson, M.D.*
Chicago, Illinois

*Director Division of Health, Service, American Medical Association, Chicago, Illinois. Former staff member, Cleveland Clinic, Cleveland, Ohio.

The Computer Versus the Clinician

THERE IS A temptation to believe, in this electronic era, that the practice of medicine in the future will be so systematized that only facts need to be fed into a properly programmed computer, and out will pop, within a matter of seconds, the correct diagnosis and details of management for the particular disorder from which a patient suffers. Alas, this 'ideal' type of armchair medicine can never come to pass, merely because computers are only as clever as the human beings who program them, and no more accurate than the human beings who feed in the data. No amount of computerized data will bring the patient to a breast biopsy if the examining physician has not felt the suspicious lump. No computer interpreting an electrocardiogram will be a substitute for the physician who is evaluating the patient with sudden chest pain and is able to observe the manifold evidences of a grave situation whose multiple components can hardly be recorded rapidly in specific measurements.

The mechanization of laboratory procedures which makes available a vast amount of laboratory information, at a nominal expense, constitutes a clear and abiding danger to the training of the young physician. The temptation will be for him to look at the laboratory reports instead of at the patient. Yet every clinician ought to have a deep distrust of laboratory data that appear to run counter to his clinical evaluation of the patient. The "S.M.A. 12" is an example of a multichannel screening device that will give determinations for twelve selected blood elements from a single blood sample. It represents a significant contribution to medical care and is an inexpensive extension of the routine blood count, urinalysis, and roentgenogram of the chest which have been a part of every complete medical examination for a great many years. Accurate information is never potentially dangerous or unwelcome (although it may be unessential), but no series of laboratory tests can give results that do more than indicate a lead to the clinician.

It is unfashionable these days to stress the importance of accurate and pertinent history taking, accurate observations of physical find-

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ings, and their correlation with relevant laboratory data by the human brain. Yet such accurate observations of the patient by the physician are the most important basis of 'scientific' medicine. We must continue to insist on the preeminent value of clinical observation and evaluation in our educational programs for physicians.

Stanley O. Hoerr, M.D.*
Cleveland, Ohio

*Chairman Division of Surgery, The Cleveland Clinic Foundation, Cleveland, Ohio.

Test Your Word Score

Rheology—*study of the flow of liquids and semisolids* (page 1036).

Revascularization—*creating new vascular channels for blood flow* (page 1039).

Nuchal—*pertaining to the back of the neck* (page 1045).

Allograft—*transplantation of an organ within a species, such as from one human to another* (page 1051).

Immunosuppressive—*having the effect of suppressing the immune reaction* (page 1053).

Hydralazine—*a sympatholytic drug* (page 1056).

Sympatholytic—*opposing the effects of impulses conveyed by adrenergic postganglionic fibers of the sympathetic nervous system* (page 1056).

Sympathomimetic—*producing effects similar to those of impulses conveyed by adrenergic postganglionic fibers of the sympathetic nervous system* (page 1059).

Anticholinergic—*blocking the passage of impulses through the parasympathetic nerves; parasympatholytic* (page 1059).

Allele—*one of a pair of hereditary characters* (page 1067).

Orthopnea—*inability to breathe except in an upright position* (page 1106).

A bullet in the leg will make a brave man a coward. A blow on the head will make a wise man a fool. Indeed, I have read that a sufficiency of absinthe can make a good man a knave. The triumph of mind over matter does not seem to be quite complete as yet.—Winston Churchill



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The Editor's Soliloquy

Like A Broken Record—The Popular Monologue

THIS ISSUE OF MINNESOTA MEDICINE is an example of the free interchange of new ideas between competing medical groups, all of whom are striving for betterment of the health of its people. In any other profession new and original ideas are secretly guarded or "protected" with copyrights* and "patents pending." To a worthy contemporary we extend our salute!

Our modern age abounds in paradoxes!

In this, the one country of the world where medical science has prospered and progressed, it has become popular to decry the medical profession for allegedly disregarding the ills of the majority because a few isolated individuals who are in need of attention will not seek out the medical aid available to them.

Rather than disparagement our American medical fraternity and its allied professions should be credited with having advanced medicine from a handful of simple specifics to thousands of life-saving drugs and procedures. True, the cost has been high; but the acceleration rate of improvement has been exponential compared with that of other types of service.*

To be sure, it is only a small but vociferous minority who constantly bark this monologue about medicine's omissions; yet they themselves usually constitute the very group who are averse to betaking themselves to the nearest center where the highest grade of medical science and technology is available without charge if the need exists. Can they be so irrational and unreasonable as to expect sophisticated and expert medical service to be available to anyone at any time at every Toonerville and crossroads where little more than first aid can be provided? Backwoods medicine and kitchen-table surgery are features of the nostalgic past: relics of frontier emergency and make-do. That frontier has now vanished; the horse-back doctor will never return. With modern speedy transportation it is far more feasible for the patient to proceed to the nearest medical center than for the doctor to go to the patient. But does the caviler blame himself for his failure to bestir himself? No indeed! He faults the medical profession, the caste system, the political establishment, the social order: any scapegoat will do!

Countries that have instituted socialized medicine have fallen far behind in medical progress; yet they cannot extricate themselves from a dilemma that has eventuated in excessive cost and inefficiency. They find their doctors padding their accounts with 40 to 50 house calls and 80 to 90 office visits daily, aggregating as many documentary blue slips to be turned in to their government for "services rendered" from patients visiting the doctor for the most part simply because of the human penchant to avail themselves of "free" service with a "bonus" of a box of tinted pills or a bottle of colored medicine posessing no more than placebo value.

Is our professional competence to be prostituted, our dedication depreciated, our independence from beadledom abnegated, our integrity stultified by a program that does not show our talents? Must we continue to administer our skill, give generously of our time and energy, maintain our equanimity, extend our compassion in the face of criticism and harassment by malcontents, who pressure to have the utopian solution for every social malady?

The day may well come when the distinguished medical profession in this country will unanimously and unequivocally repudiate the nefarious charge of medical inadequacy and inequity and insist on their prerogative of providing medical care in one way only: their own manifestly knowledgeable way.

Carl O. Rice, M.D.

*See copyright permission page 1027.
†See Table page 1162.

Old Doc Hess says: Behold in that individual a lustrous pearl in humanity's necklace of wisdom!—COR

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Curbstone Consultation

Anorexia Nervosa

QUESTION: Is anorexia nervosa a single entity or does that diagnosis imply a more serious psychiatric problem such as schizophrenia? Do these children ever get completely well?

ANSWER: There are many variations of anorexia nervosa, but with weight loss, amenorrhea, excessive exercise, dieting, vomiting, and above all, an unconscious and sometimes conscious rejection of adult femininity (or rarely masculinity), I should call it a discrete entity. Quite often these individuals become schizophrenic, but as likely as not they are severely obsessive-compulsive persons. They can get "completely well," but it does not happen often.

Richard B. Markey, M.D.*
Cleveland, Ohio

*Department of Psychiatry, The Cleveland Clinic Foundation, Cleveland, Ohio.

'Living Virus'

QUESTION: Would you comment on Doctor Kornberg's synthesis of a 'living virus'? Do you really think there is a possibility of changing the genetic structure of human lungs?

ANSWER: There is no doubt that Doctor Kornberg's synthesis of an active, disease-producing virus represents a major landmark in the history of medical research. However, since the "living" nature of viruses is still controversial, and since his synthesis required the presence of an active, naturally occurring enzyme, it should not be construed as the first "test-tube" synthesis of life. Doctor Kornberg himself has emphasized this point. The major significance of his work is that it opens the possibilities to enable man, some day, to induce genetic alterations at will. The potential applications of such a procedure in the practice of medicine would be limitless.

Sharad Deodhar, M.D., Ph.D.*
Cleveland, Ohio

*Division of Pathology, The Cleveland Clinic Foundation, Cleveland, Ohio.

Inactivated Measles Vaccine

QUESTION: What is the concern about the use of inactivated measles vaccine and why has the Committee on Control of Infectious Diseases of the American Academy of Pediatrics advised it be discontinued?

ANSWER: Unusual systemic reactions have been noted in patients who have come into contact with natural measles when they have previously received the inactivated vaccine. Also, in some of these persons receiving live attenuated vaccine, after previous exposure to the inactivated vaccine, a local reaction has been seen at the site of the injection. Reactions of this sort have not been observed in persons who have received only the live vaccine.

Derrick Lonsdale, M.D.*
Cleveland, Ohio

*Department of Pediatrics, The Cleveland Clinic Foundation, Cleveland, Ohio.

Ulcerative Colitis and Emotional Disturbance

QUESTION: What are the present thoughts concerning the relationship of ulcerative colitis and emotional disturbances? Is an emotional disorder the cause of ulcerative colitis?

ANSWER: The etiology of ulcerative colitis remains unknown. The association of emotional problems in some children with ulcerative colitis is noted, but, in others, obvious emotional conflicts are absent. Attempts to treat the family emotional conflicts as the primary therapy of the child with ulcerative colitis have not resulted in medical improvement of the child. In fact, in the initial therapy of the child with ulcerative colitis, if emotional causes of the disease are openly alluded to, the physician may actually hinder his ability to treat the child. Until more is known regarding the etiology of this disease, the medical therapy of the child with ulcerative colitis must be flexible and focused on treating the whole child.

William M. Michener, M.D., M.S.(Pediatrics)*
Albuquerque, New Mexico

*Formerly member of the staff, Department of Pediatrics, Cleveland Clinic; present address: University of New Mexico Medical Center, Albuquerque, New Mexico.

Early Active Rheumatoid Arthritis

QUESTION: How do you manage patients with early active rheumatoid arthritis who respond satisfactorily to treatment except for persistent pain and swelling of ankles?

ANSWER: This condition is usually due to chronic foot strain resulting from a flexible or depressed longitudinal arch, which in turn causes tenosynovitis of the tibial and peroneal tendon sheaths. Treatment is directed toward elimination of mechanical stress forces on the involved tendons. Well-fitting shoes with adequate arch supports should be worn at all times. Heel and sole wedges are used when indicated. Walking barefoot or in soft slippers is discouraged. Daily physical therapy, including contrast baths and foot and leg exercises and correct posture in standing and walking, is emphasized. These patients should avoid standing or walking for long periods, and weight reduction is prescribed when indicated. It is important to advise these patients to carry on with proper foot care indefinitely, in addition to any other therapeutic measures that are used.

Arthur L. Scherbel, M.D.*
Cleveland, Ohio

*Department of Rheumatic Disease, The Cleveland Clinic Foundation, Cleveland, Ohio.

Infected Intervertebral Disk

QUESTION: What are the diagnostic features of an infected intervertebral disk?

ANSWER: One must be suspicious of a disk infection in any patient with severe back pain accompanied by frequent incapacitating episodes of muscle spasms affecting the back, legs, and even the abdomen. Precipitation of the episode by even the slightest jarring has led to the use of the "bed-jarring" test. The attacks are so dramatic that these patients are often thought to be hysterical. The history of recent systemic infection, especially urinary, is often obtained. Frequently there has been some type of spinal or paraspinal needling in the recent past. Unfortunately, changes caused by infection are usually not apparent roentgenographically for from six to eight weeks. The sedimentation rate is increased in most patients, but the leukocyte and differential counts usually are normal.

Donald F. Dohn, M.D.*
Cleveland, Ohio

*Department of Neurologic Surgery, The Cleveland Clinic Foundation, Cleveland, Ohio.

Disease as Reprisal

What threats of horrendous retribution did the Lord make to those who might fail to keep his covenant?

The Lord shall make the pestilence cleave unto thee, until he have consumed thee from off the land, whither thou goest to possess it.

The Lord shall smite thee with a consumption, and with a fever, and with an inflammation, and with an extreme burning, and with the sword, and with blasting, and with mildew; and they shall pursue thee until thou perish.

The Lord shall smite thee with the botch* of Egypt, and with the emerods†, and with the scab, and with the itch, whereof thou canst not be healed.

The Lord shall smite thee with madness, and blindness, and astonishment of heart.

The Lord shall smite thee in the knees, and in the legs, with a sore botch that cannot be healed, from the sole of thy foot unto the top of thy head.

Then the Lord will make thy plagues wonderful, and the plagues of thy seed, even great plagues, and of long continuance, and sore sicknesses, and of long continuance.

Moreover he will bring upon thee all the diseases of Egypt, which thou wast afraid of; and they shall cleave unto thee.

Also every sickness, and every plague, which is not written in the book of this law, them will the Lord bring upon thee, until thou be destroyed. (Deuteronomy 28:21, 22, 27, 28, 35, 59-61)

*Botch—sores
†Emerods—hemorrhoids

DERIVATIVELY SPEAKING

Nidus—from Latin *nidus* (a nest).

A wise man knows everything; a shrewd one, everybody.—Anonymous

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Initiate therapy with **Hydromox*** Quinethazone 100 mg. (two 50 mg. tablets) daily for 15 days



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Precautions: Electrolyte abnormalities may be aggravated or produced. Caution is important during prolonged or intensive therapy and when salt intake is restricted. Hypokalemia has been mild and infrequent, and other electrolyte abnormalities rare. The possibility of potassium depletion and its toxic sequelae must be kept in mind, particularly in cirrhotics and patients receiving digitalis. As a preventive measure the use of foods rich in potassium, such as orange juice, may be desirable. Although not a thiazide, HYDROMOX may possess certain characteristics of the thiazides. They have been known to cause jaundice with liver involvement and pancreatitis; hematological complications such as purpura with or without thrombocytopenia and leukopenia (neutropenia); increases of serum uric acid; decreased glucose tolerance as evidenced by hyperglycemia and glycosuria thus aggravating or provoking diabetes mellitus and azotemia in patients with renal disease: photoallergy. Discontinue use a few days prior to elective surgery. When added to a regimen that includes ganglionic-blocking agents, the dosage of these latter preparations should be reduced. Also reduce dosage when one or more of these antihypertensive agents is added to an established HYDROMOX regimen. Contraindicated in anuria. Observe for possible hematologic complications.
Side Effects: Skin rash; gastrointestinal disturbances (chiefly nausea), weakness, dizziness. These seldom require cessation of therapy, and can be relieved by reducing dosage or correcting electrolyte imbalance.
Warning: Enteric coated potassium tablets have been implicated in small bowel lesions and should be used only when adequate dietary supplementation is not practical.

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401-8



Fracture-Trauma Conference

The Patient with Multiple Fractures

THE PRESENT epidemic of trauma—especially from auto accidents— has increased the importance of the management of patients with multiple injuries. This fracture trauma conference illustrates the principles involved in the care of the severely injured patient, including the treatment of hemorrhagic shock and the management of open fractures.

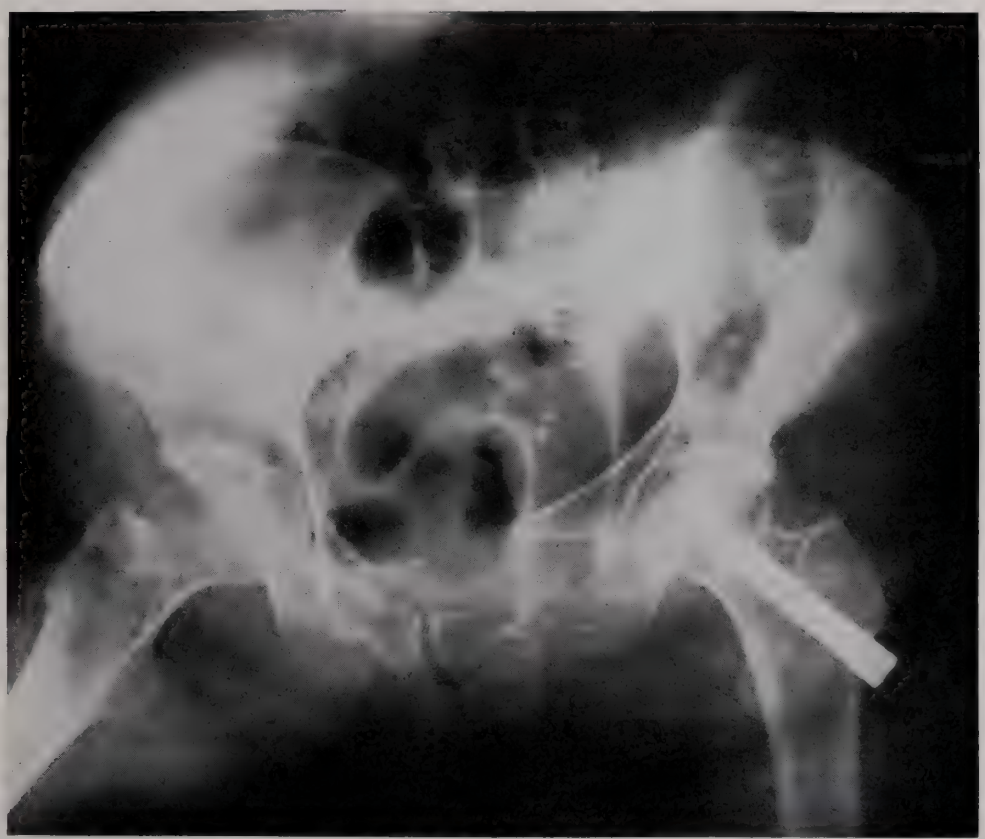


Fig. 1—Fractures of superior and inferior pubic rami bilaterally, subluxation of left sacroiliac joint.

Dr. Karl S. Alfred:* **Case History**

On the evening of March 3, 1967, a 79-year-old Caucasian seamstress for a dry cleaning company was brought to the emergency room of St. Vincent Charity Hospital with a large compound wound of the inner aspect of the left thigh and with several inches of femur protruding from the wound. The patient was fully conscious, and stated that she had been struck by an automobile while waiting for a bus and that the vehicle had run over both her legs. She had just left a church service and was standing at the bus stop when she was struck. The accident occurred just a few blocks from the central police station and the patient was brought to the hospital by police ambulance within minutes from the time of the accident. She had pain in both legs and the lower part of the abdomen. As stated above, there was a large wound of the inner aspect of the left thigh with 3 or 4 inches of the proximal left femur protruding. There was tenderness over the groins and the lower aspect of the right thigh. The blood pressure was 156/110 mm Hg, pulse rate 112, blood hemoglobin content, 12.1 g per 100 ml, hematocrit 39, and a catheterized urine specimen was clear. Anti-gas-gangrene and tetanus medication was administered immediately, as well as 1 g of streptomycin and 2,000,000 units of penicillin. Roentgenograms of the chest, abdomen, pelvis, and both thighs were obtained; these revealed multiple fractures of the pelvis with subluxation of the left sacroiliac joint and an old healed fracture of the neck of the left femur, with the Smith-Petersen nail still in place (Figure 1). Figure 2 shows the compound fracture of the left femur with displacement of the proximal fragment and its exit through a large medial thigh wound. Figure 3 reveals a fracture of the right medial femoral condyle in good position.

Evaluation of the patient's condition resulted in the decision to operate on the large compound bleeding wound of the left femur. The patient was typed for blood and cross-matched, and an infusion of a unit of dextran was started in the emergency room. In the operating room the blood pressure was imperceptible, and the pulse weak though fairly constant. With the anesthesiologist and surgical team observing the patient and treating the shock, she began

*Chief of Orthopedic Department, St. Vincent Charity Hospital, Cleveland, Ohio.



Fig. 2—Left femoral shaft fracture with protrusion of proximal fragment through medial thigh wound.

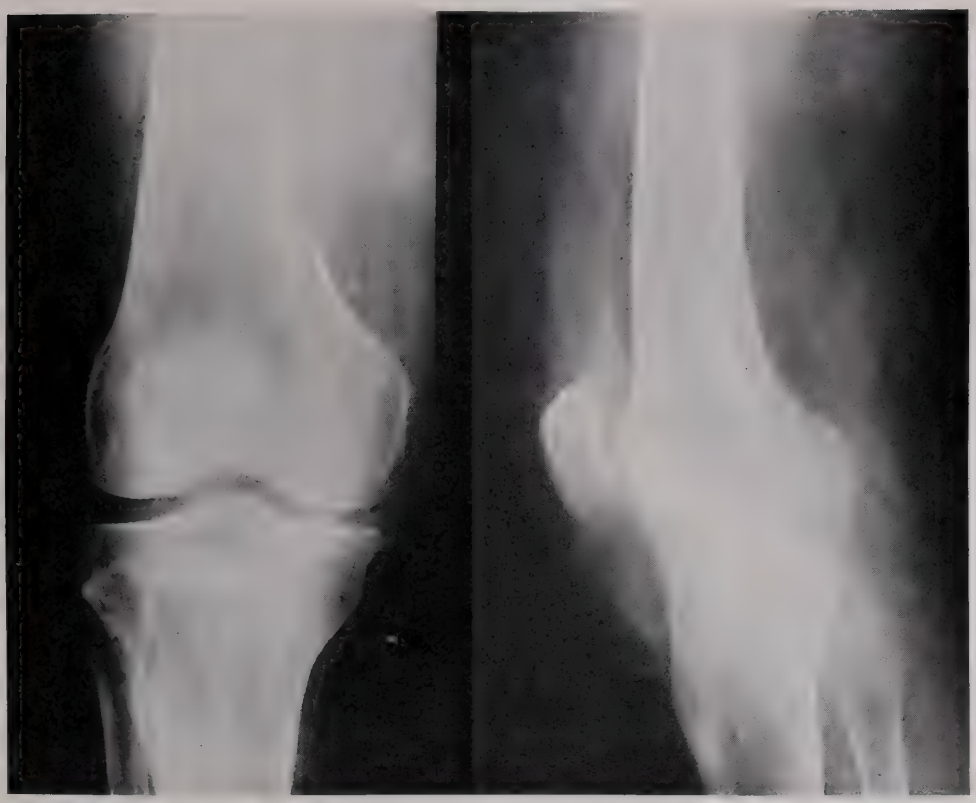


Fig. 3—Fracture of right medial femoral condyle with minimal displacement.

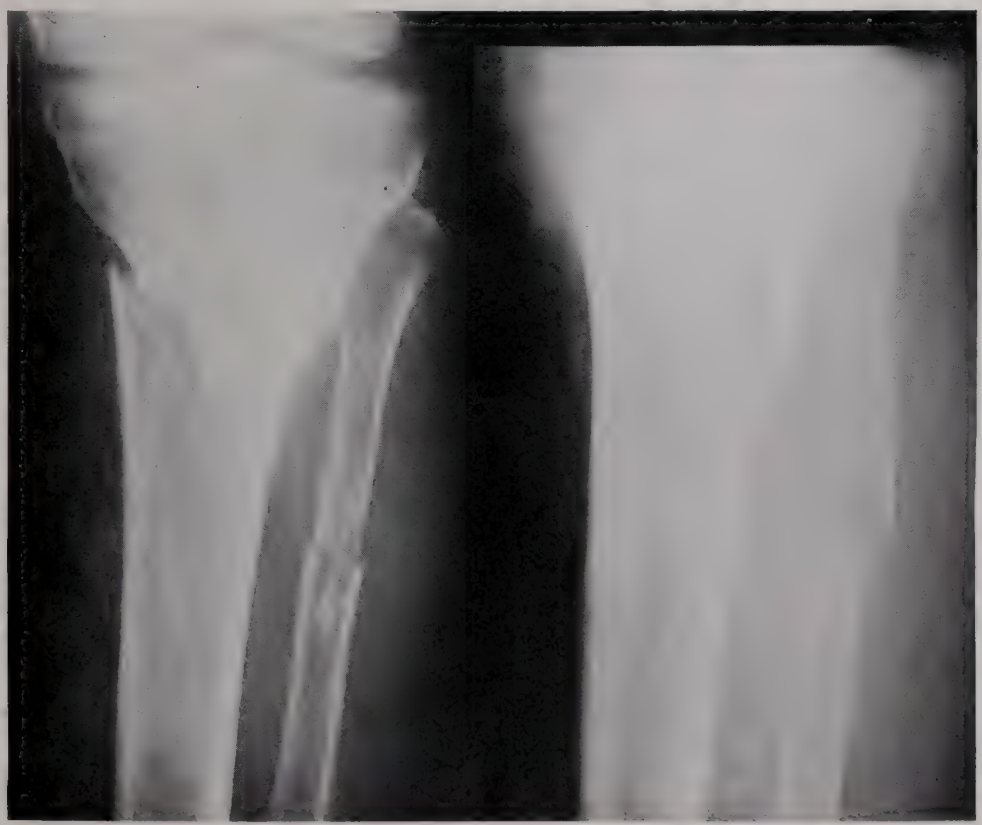


Fig. 4—Fracture of proximal portion of left tibia and fibula.

to rally after a second unit of dextran and the administration of whole blood. When the blood pressure stabilized at 120/80 mm Hg, and the pulse became full and regular, definitive treatment was considered. Several units of blood were in readiness, and the patient's status was considered sufficiently satisfactory for administration of a general anesthetic and a short surgical procedure, provided it would not add too much more trauma. Under general anesthesia the patient's condition remained stable. The left thigh revealed a large laceration of the skin and subcutaneous tissues, and the proximal femur protruding through a large wound in the vastus medialis and adductor muscles. After superficial wound debridement and irrigation, the patient's condition was still stable. Further exploration revealed that the distal femoral fragment was easily accessible in the deeper aspects of the wound; both fragments could easily be grasped with bone-holding forceps. Despite the presence of the nail in the neck of the left femur it was decided that it would be feasible to stabilize the femur with an intramedullary nail, with the only further trauma being a small stab wound to remove the nail, and the retrograde incision above the hip for the intramedullary nailing. The Smith-Petersen nail was easily removed with a Kocher clamp by palpation through a 1-inch incision, and a Schneider intramedullary nail was driven into the proximal fragment and then into the distal fragment without further dissection. Fixation was excellent and the wounds were closed primarily. At the conclusion of the procedure the patient had received two units of dextran, three units of blood, and her blood pressure was 130/90 mm Hg. At this time, with the left femur stabilized, crepitus was palpable and abnormal motion demonstrable just below the left knee. Roentgenograms revealed a fracture of the proximal portion of the left tibia and fibula (Figure 4). Massive long-leg "soft casts" were applied, and the patient was in good condition when she left the operating room. She received a fourth unit of blood in the intensive care unit and a total of 1000 ml of lactated Ringer's solution, and 500 ml of 5% dextrose in ¼% normal saline solution. The blood pressure remained stable around 100/70 mm Hg all night.

The next day the blood hemoglobin content was 9 g per 100 ml. hematocrit 25, pulse rate 72, respirations 20; and the blood pressure fell to 90/60 mm Hg. She was given another unit of blood in addition to other supportive measures. The urine output decreased to 50 ml in eight hours, and the blood urea nitrogen (BUN) was 27 units. She was given mannitol, and the urine output increased to 90 ml per hour. Urine output remained good and the BUN decreased. During the next five days, after a further decrease in hemoglobin content to 8.5 g per 100 ml, she was given five more units of blood, and on March 9, 1967, six days after the injury, her hemoglobin content was 12.1 g per 100 ml, and the hematocrit 36. She had received a total of 10 units of whole blood and her condition was good. Figure 5 shows the position of the pelvic fractures at that time, and Figure 6, the left femoral shaft fracture.

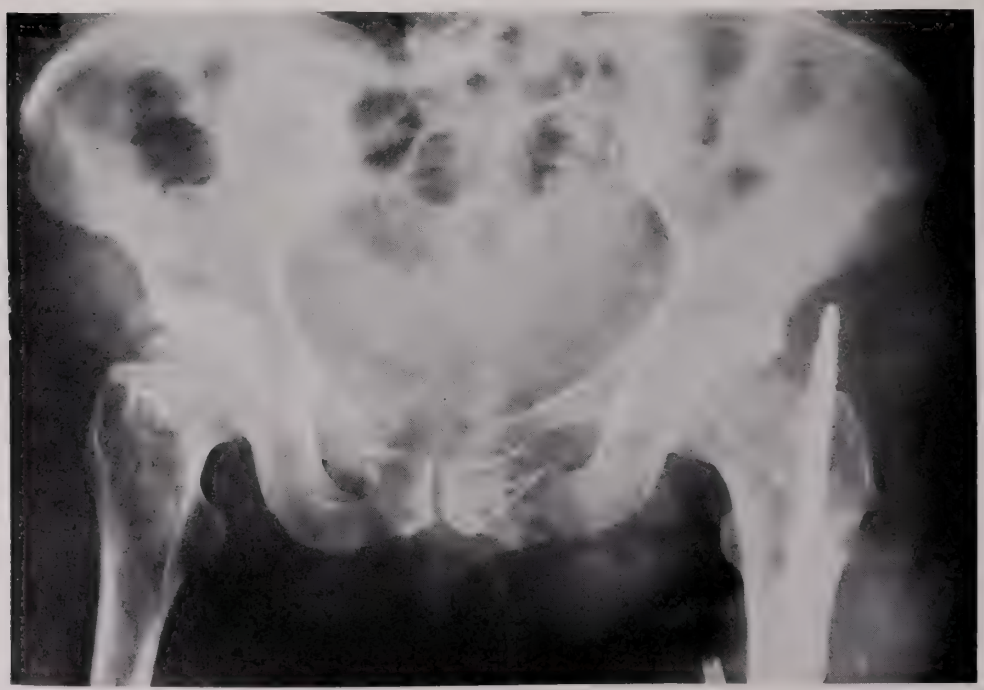


Fig. 5—Postoperative view of pelvis and proximal portion of Schneider nail in left femur.

After the initial doses of streptomycin and penicillin, she was treated with erythromycin and then chloromycetin. The temperature curve was persistently elevated, but the leukocyte count remained low and there were no signs of infection. Vomiting and diarrhea developed, and medical consultation was obtained on March 16, 1967. No definite cause for the fever or the vomiting and diarrhea could be determined, but medication was changed to mystatin which was maintained from March 17 to March 23, 1967; and thereafter she was given amphocillin q.i.d. from March 27 to March 30, 1967. The symptoms subsided. On March 27, 1967, about three and one-half weeks after the injury, she was given a general anesthetic, and posterior plaster splints were applied with massive compression bandages. The left thigh wound and the surgical wounds about the left hip had healed per primum. She had a superficial sacral pressure sore and also severe excoriation of the perineum, both of which lesions cleared under local treatment with alum and heat. There were massive ecchymoses of the buttocks and pelvis, but with no skin lesions. The plaster leg splints were applied so that the patient could be mobilized, and on March 31, 1967, four weeks after the injury, she sat in a chair for the first time. Figure 7 shows the position of the left tibia and fibula fracture in a posterior plaster splint.

For the next two weeks the patient continued to improve, but then again developed a temperature elevation and pain in the right lower abdominal quadrant, with localized tenderness. On April 18, 1967, exploratory operation over the right lower quadrant revealed only sterile



Fig. 6—Excellent position of left femoral shaft fracture with intramedullary fixation.

amber fluid. Cultures of the fluid were negative. There was no intraabdominal pathology. The patient's condition improved, and on April 25, 1967, the right leg cast was removed and she was started on physiotherapy, with progressive weight-bearing on the right leg on the next day. On April 28, 1967, the left leg splint was removed and physiotherapy was continued with progressive weight-bearing on both legs. The patient had spent her eightieth birthday in the hospital and she was discharged on May 24 1967, ambulatory and in good condition. Figures 8, 9, and 10 show that the fractures of the pelvis, left femur, left tibia and fibula, and right medial femoral condyle had healed well after nine months. The Schneider nail was removed on January 8, 1968. Despite her multiple severe injuries and her 80 years the patient intended to return to work as a seamstress.



Fig. 7—The left tibia and fibula fracture in posterior splint.

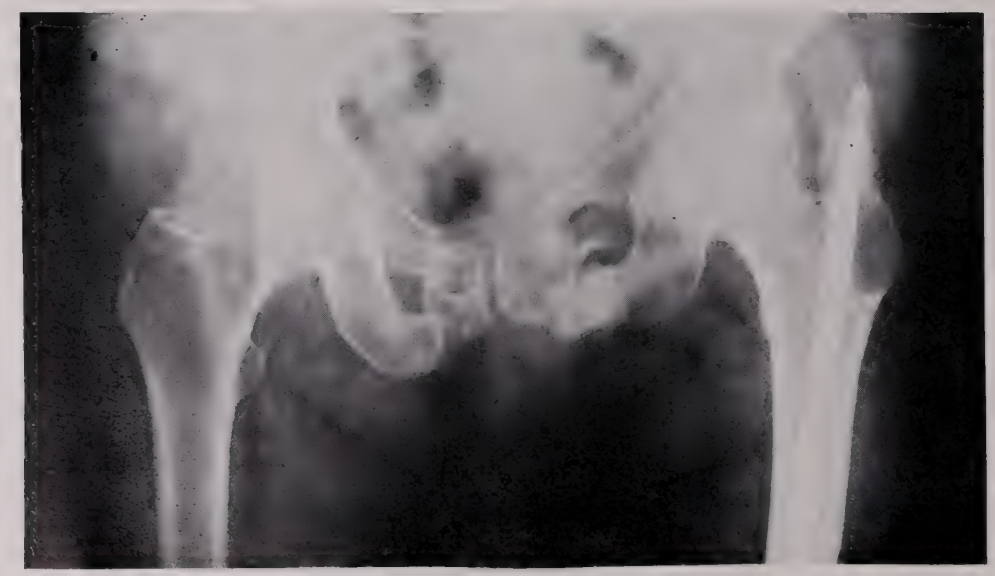


Fig. 8—Healed pelvic fractures nine months after injury.

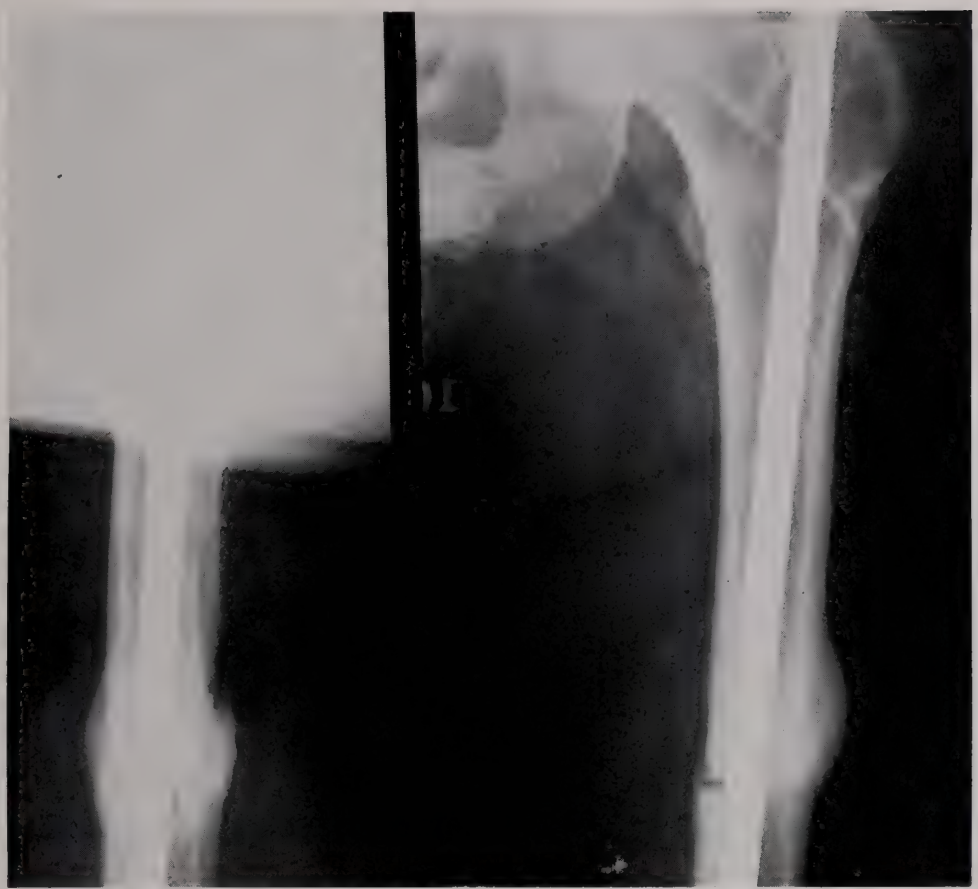


Fig. 9—The left femur nine months after injury.

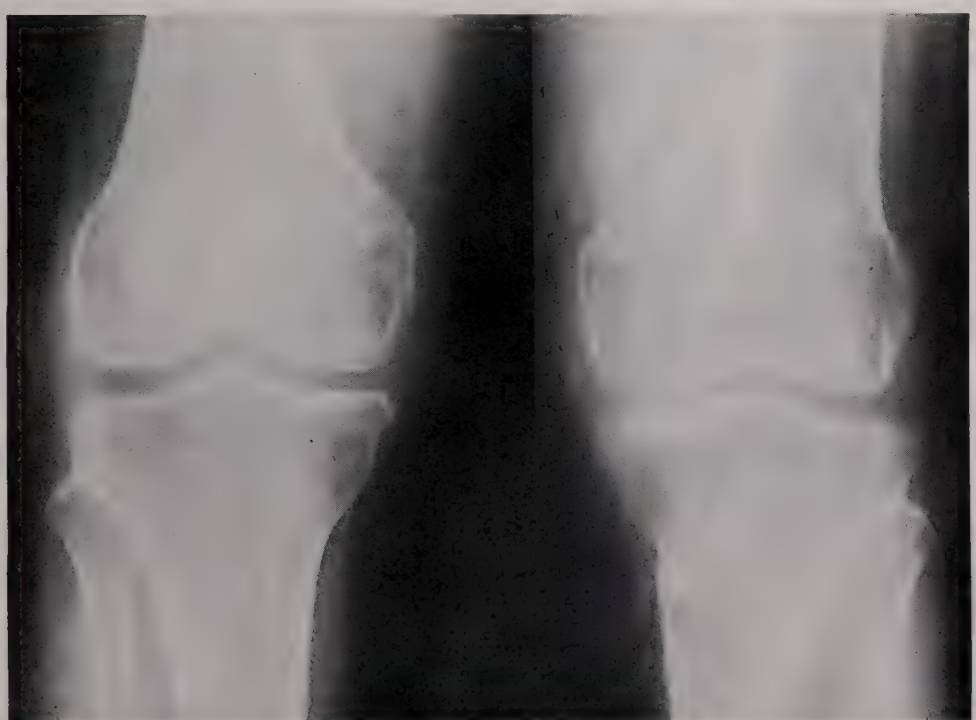


Fig. 10—At nine months after injury the fractures of the right medial femoral condyle and proximal portions of the left tibia and fibula are well healed.

Discussion

This is a presentation of a case in which the patient had multiple major fractures treated successfully by first controlling the shock and then proceeding with rapid definitive treatment of the femoral shaft fracture by internal means and supportive treatment of the other fractures. Close observation of the patient in the intensive care unit during the first week was most important to the success of the treatment. The patient had lost a considerable amount of blood from the compound wound. Also, a pelvic fracture alone in this age group can be a severe injury, and in itself sometimes fatal. Dr. Gustafson, would you comment on the shock treatment?

Dr. Gordon E. Gustafson:*

The initial blood pressure in the emergency room was 156/100 mm Hg. Because of blood loss from the numerous fractures, the blood pressure dropped to 40 mm Hg systolic. Shock was treated initially with two units (1000 ml) of dextran, followed by whole blood. The blood pressure had stabilized at about 120/80 mm Hg at the time the patient arrived in the operating room two hours after her arrival in the emergency room. The third unit of blood had been administered at the conclusion of the operation, about four hours after her arrival in the emergency room. Postoperatively there was a brief period of anuria which responded promptly to the rapid injection of 25 g of mannitol, and to the increased rates of fluid administration and blood replacement to 125 and 200 ml per hour, respectively. Urine excretion started promptly, and subsequently ranged from 30 to 75 ml per hour. Six units of whole blood, 1000 ml of dextran, 1000 ml of lactated Ringer's solution, and 500 ml of 5% dextrose in ¼% normal saline were administered in the first 16 hours. Fluid administration was subsequently decreased to 100 ml of 5% dextrose in ¼% normal saline. The vital signs remained stable thereafter.

The last decade has seen a change in the treatment of hemorrhagic shock. Formerly, emphasis was directed toward the maintenance of an adequate blood pressure. Currently, therapy is directed toward adequate tissue perfusion. Blood pressure and pulse continue to be important parts of the evaluation of any patient with acute hemorrhage. However, the administration of vasopressor drugs is no longer considered good treatment, as these drugs reduce tissue perfusion.

The goal of shock treatment is restoration of adequate tissue perfusion at the cellular level. Blood pressure, pulse, central venous pressure, urinary output, cardiac output, total peripheral resistance, stroke volume, mean transit time, central blood volume, arterial oxygen saturation, and venous oxygen saturation are all helpful indexes of tissue perfusion. Blood pressure, pulse, urinary output, and central venous pressure are most readily measurable, and are helpful in the evaluation of the status and treatment of shock. The measure of urinary output is of great value. If blood pressure is sufficient to maintain an adequate urinary output, tissue perfusion is adequate to maintain the kidneys and probably other organs as well. Central venous pressure is valuable as an index to fluid and blood replacement. If central venous pressure is low, it indicates inadequate replacement. If central venous pressure is elevated, the patient should be watched for right-sided heart failure.

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A large-bore catheter should be inserted into the central venous system in every seriously injured patient at the time of initial venipuncture. At the same time, a sample of blood should be withdrawn for typing and cross-matching. The catheter can be used for the rapid infusion of fluid and whole blood as well as for the measurement of central venous pressure. A catheter should also be inserted into the bladder. If urinary output does not start promptly, mannitol should be given in addition to adequate fluid and blood replacement.

The appropriate anesthetic in these patients is cyclopropane, because it permits the body to maintain its reflex compensations for a maximal period. It also is a very rapidly reversible agent.

Dr. Alfred:

Due credit in this case must be given to the resident staff in their diligence and astute observation in the postoperative course and management.

Dr. James I. Kendrick:*

Do you think prior knowledge of the left tibia and fibula fractures would have altered your treatment?

Dr. Alfred:

I don't think so. Treating the femoral fracture by traction would require skeletal traction preferably through the tibial tubercle. The fracture of the tibia obviated this. Actually, stabilizing the femoral fracture rendered the treatment of the tibial fracture that much easier. I think the only thing that may have prevented the intramedullary approach would have been a much greater procedure about the hip, such as extensive surgery to remove a nail and plate. As it was, the Smith-Petersen nail was plucked out through a small stab wound, with minimal trauma.

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Cleveland, Ohio

*Department of Orthopedic Surgery, The Cleveland Clinic Foundation, Cleveland, Ohio; and St. Vincent Charity Hospital, Cleveland, Ohio.

†Department of Orthopedic Surgery, The Cleveland Clinic Foundation, Cleveland, Ohio.

Have Faith

Personally, I should always prefer the patient who believes something, as contrasted to the patient who believes nothing. Give me the patient who believes that a chunk of asafetida worn on a string around the neck will ward off disease, in preference to the patient who sits in complete resignation.

We may sneer at the ridiculous practices of the past, when surgery was a sideline for the town barber and when therapy consisted of little more than bloodletting. And yet many a service man who saw duty in North Africa during World War II, returned with strange stories of the practice of bloodletting among some of the unenlightened Arabs—and even stranger stories of recovery. But are they really any stranger than the stories from our own country, where a distinguished surgeon will have a higher percentage of recoveries at the Mayo Clinic than he will have after returning to his own hospital in Schenectady or Portland? He uses the same skills and the same technique, and possibly he has identical equipment at his command. But the reputation of the Eighteenth Street Hospital doesn't inspire so much faith as does the magic name of the Mayo Clinic in Rochester. And that makes a difference that can be measured in percentages, in the vital statistics column.*

*James Fisher, M.D.: A Few Buttons Missing, 1951.



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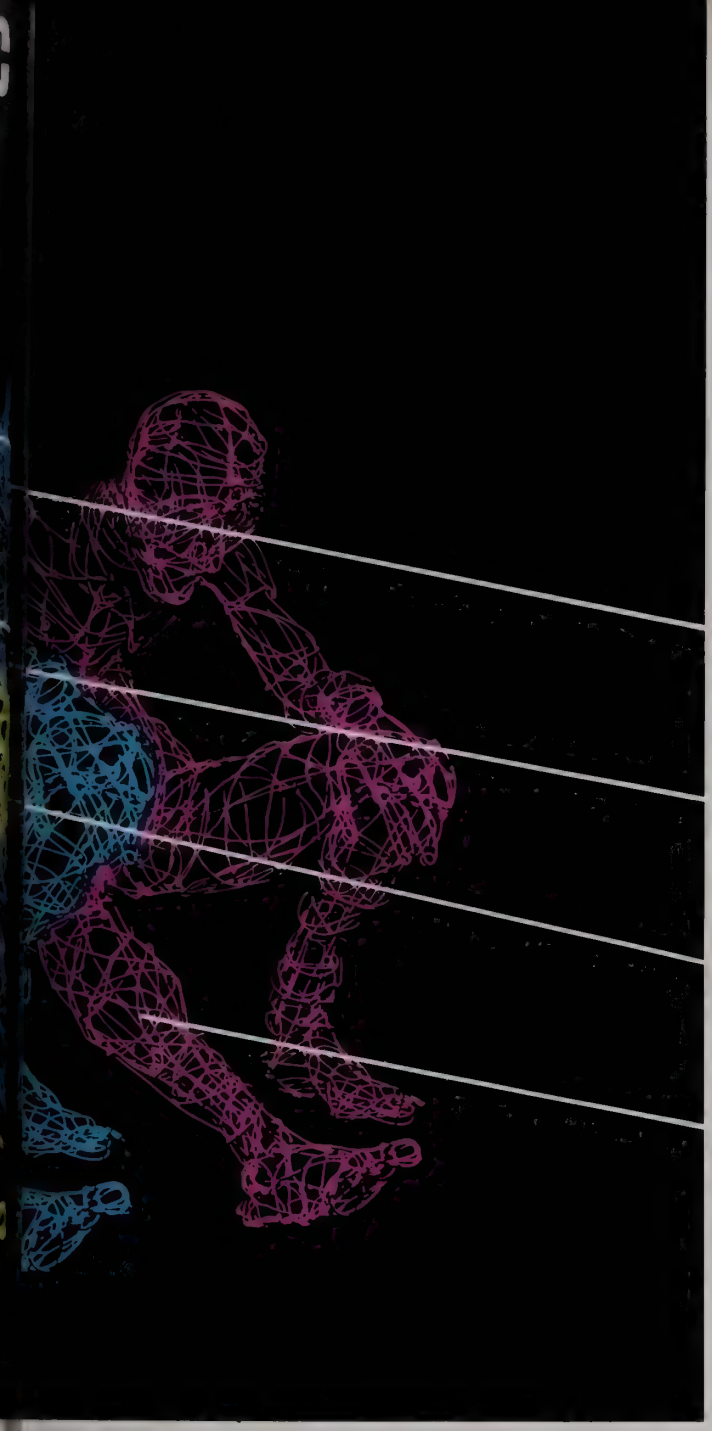
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Clinical Path Conference

Weakness and Chronic Heart Failure

Case History

History

A 50-year-old white woman who worked as a bookkeeper was first examined at the Cleveland Clinic on August 17, 1966. She was referred by her family physician because of his difficulty in controlling her congestive heart failure, and his concern about her electrocardiogram that had been interpreted as showing dextrocardia with left ventricular and left atrial enlargement. Her medications included digitoxin, 0.1 mg daily, and a diuretic several times weekly, with potassium supplements.

When she was first seen, the chief complaint was related to extreme weakness of the arms; this was so severe that she could hardly elevate them to comb her hair. She was also experiencing shortness of breath with exertion and had noted intermittent swelling of the feet and ankles. She had been unable to work for four months—since May of 1966.

This illness began in November of 1965, when she first noticed fatigue, weakness, and shortness of breath. These symptoms progressed slowly during the ensuing six months. In addition, anorexia developed and she lost 20 pounds. In May, 1966, the patient was admitted to a hospital in her community, where she remained for two weeks. She was told that there was too much fluid in her lungs because of rheumatic heart disease. She was treated for congestive heart failure, with a resultant additional loss of 10 pounds, disappearance of ankle swelling, and some improvement in breathing. However, the weakness persisted and she was unable to return to work.

Physical Examination

When first seen at the Cleveland Clinic, her weight was 130 pounds, her height, 68 inches. The blood pressure (sitting) was 90/60 mm Hg; the pulse was 78 beats per minute and regular; the oral temperature was 98F. She appeared pale, wan, and chronically ill. The pertinent physical findings were as follows: the neck veins were slightly distended; the lungs were clear; the heart was enlarged, with the point of maximal impulse located in the fifth left intercostal space at the left anterior axillary line; the heart sounds were of fair quality with an increase in the intensity of S_1 at the apex; there was normal splitting of S_2 at the base, and S_2 at the pulmonic area was slightly increased; there was an early diastolic sound audible at the apex; no murmurs were heard; there was no palpable enlargement of the liver or spleen; the extremities were not edematous; the peripheral pulses were full.

Laboratory Proceedings

A roentgenogram of the chest showed 25 percent generalized cardiac enlargement according to the Ungerleider scale. The enlargement was thought to be primarily right ventricular with slight left atrial enlargement. There was an increase in peribronchial markings in both lungs. Fluoroscopy confirmed these impressions. No intracardiac calcifications were noted.

On August 19, 1966, the electrocardiogram showed considerable right axis deviation with relatively large R waves in the right precordial leads. The T waves were diphasic in leads II, III, and AVF, and were inverted in leads V5 and V6.

Results of initial laboratory studies included the following: hemoglobin, 11.9 g/100 ml; cell volume percentage, 37; a leukocyte count of 9,200 per cubic millimeter, and a normal differential count; normal platelets. Urinalysis—pH, 6.5; specific gravity, 1.008; protein, 2 plus; sugar, 0; erythrocytes, many; leukocytes, 10 to 15; casts, 0. Fasting blood sugar, 68 mg per 100 ml; serologic tests negative; sedimentation rate (corrected), less than 0.05 mm/min.

In order to continue diagnostic studies, including cardiac catheterization, she was admitted to the Cleveland Clinic Hospital on September 16, 1966. In the hospital the following additional laboratory data were obtained: serum sodium, 141 meq per liter; serum potassium, 4.5 meq per liter; serum chloride, 102 meq per liter; carbon dioxide, 25 meq per liter; blood urea, 30 mg per 100 ml; urinalysis—3 plus protein; specific gravity, 1.010; 8 to 10 erythrocytes per high-power field; 15 to 20 leukocytes per high-power field; urine culture, sterile; 12-hr Addis count (wet) showed: volume, 760 ml; specific gravity, 1.009; pH, 6.0; protein, 1.44 g per liter or 2.188 g per 24 hr; more than 50 million erythrocytes and leukocytes per 24 hr. The lupus erythematosus cell test was negative. Serum protein electrophoresis—total, 5 g per 100 ml, with 3.7 g albumin; α_1-globulin, 0.3 g; α_2-globulin, 0.3; β-globulin, 0.5 g; γ-globulin, 0.3 g per 100 ml.

Phonocardiography revealed that the early diastolic sound occurred 0.16 second after the second heart sound. An excretory urogram showed normal renal function; the kidneys were not enlarged, and there was a small stone in the inferior calyx of the right kidney.

On September 22, 1966, left- and right-sided heart catheterization studies were done, and cinecoronary angiograms were obtained.

On September 27, 1966, thoracotomy was performed. Oliguria developed postoperatively, with increases in blood urea to 129 mg per 100 ml, blood creatinine to 4.4 mg per 100 ml, and potassium to 6.8 meq per liter. On the fourth postoperative day, while she was being prepared for hemodialysis, cardiac arrest occurred, and despite all attempts at resuscitation, the patient died.

Evaluation

Paul Nickerson, M.D.*:

In discussing the cause of this patient's disease, I believe that several basic questions must be considered before some of the details can be mentioned. First of all, did this syndrome appear at first glance to fit into any one particular grouping of heart disease? Did it seem to be coronary artery disease, myocardial disease, a valvular or structural defect? What role did the lungs or kidneys play in this process, as well as isolated factors such as hypertension or neoplastic obstruction? The history seemed to be rather nonspecific, and, except for an enlarged heart, a diastolic sound, and some variation in the normal intensity of heart sounds on auscultation, few other pertinent findings were elicited. Perhaps more important were the negative findings, which included no chest pain, fever, irregular heart rhythm, high blood pressure, hemoptysis, syncope, cyanosis, heart murmur, orthopnea,† nocturnal dyspnea, or familial heart disease.

Upon initially reading the protocol, the possibility of *primary or secondary myocardial disease* is certainly brought to mind. The evidence of persistent cardiac failure, despite digitalization and repeated diuresis, and the absence of a heart murmur would suggest that primary or secondary myocardopathy was present in this patient. The insidious onset of weakness and fatigue, dyspnea on exertion, and the presence of what can be assumed to be a ventricular diastolic gallop are consistent with this disease, even though these find-

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†See Test Your Word Score Page 1083.

ings are nonspecific. Many patients (approximately two thirds) with myocardopathy have systolic murmurs, mainly mitral in origin. They also have other signs and symptoms such as arrhythmia, syncope, and pleuritic or anginal pain. Since the patient we are discussing had none of these signs or symptoms, it seems unlikely that she had primary myocarditis.

Chronic pericarditis is usually of gradual onset and can have presenting symptoms similar to those in this case. Certainly absence of chest pain, and presence of a diastolic sound or knock, without a murmur, could be associated with chronic pericarditis. An electrocardiographic pattern resembling the changes seen in right ventricular hypertrophy, a low blood pressure, decreased pericardial pulsations as shown by fluoroscopy, and an enlarged heart shadow on the roentgenogram are other signs consistent with chronic or constrictive pericarditis. However, the absence of a low-voltage QRS and pericardial calcifications, militate against a diagnosis of chronic pericarditis in this patient.

Another diagnosis that should not be overlooked is that of *arteriosclerotic heart disease*. Arteriosclerotic heart disease can become evident by cardiac enlargement with congestive failure without prior warning from angina or myocardial infarction, even though this mode of onset is unusual. However, this patient lacked even the indirect evidence of such a possibility. She had a normal fasting blood sugar value, no hypertension, no metabolic disease, and there is no mention of a positive family history of arteriosclerosis. A blood cholesterol value was not determined, and the presence of arcus senilis was not mentioned. It might be expected that the presence of extreme right axis deviation and evidence of predominant right ventricular hypertrophy, as noted in this patient, would be extremely rare. At this time it would be well to examine the roentgenograms.

Radiology

William R. Pudvan, M.D.*:

Two sets of roentgenograms of the chest of this patient are available; the first set was taken in August of 1966, and the second approximately five weeks later. The chest findings are interesting, inasmuch as there are moderate cardiomegaly and a straightening of the left cardiac border, suggesting prominence of the pulmonary artery segment in this region. The configuration of the heart would suggest right ventricular enlargement, particularly on the left anterior oblique view, since an increased transverse cardiac diameter is seen. I am not convinced that there is much evidence of left ventricular enlargement present on these films. In addition, on the right anterior oblique view, the barium-filled esophagus is not abnormally displaced or deviated; so, although there is evidence of enlargement of the right side of the heart and a prominent pulmonary artery segment, I see no evidence of left atrial enlargement. In the lung fields, there are prominent pulmonary vascular markings extending all the way to the lateral chest walls and, in addition, some septal lines that can be seen, particularly in the right costophrenic angle.

These findings would indicate pulmonary venous hypertension. This, plus enlargement of the right side of the heart, would certainly suggest mitral involvement. In the absence of definitive evidence of an enlarged left atrium, it is interesting to speculate that something might be interfering with the patient's pulmonary venous return. If I am correct in assuming that the left

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atrium is not enlarged, I would suggest on the basis of these roentgenograms that the interference is proximal to the mitral valve, either within the left atrium and not causing enlargement, or, proximal to that, some type of lesion affecting the pulmonary venous system. The second set of roentgenograms merely shows an accentuation of these findings, with moderate increase in heart size and increased prominence of the septal lines suggesting pulmonary venous hypertension. From the radiologic viewpoint alone, I would favor a diagnosis of myxoma of the left atrium; my second choice would be mitral stenosis.

Doctor Nickerson:

Would you show the electrocardiogram, please?

This tracing shows extreme right axis deviation; I estimate it to be about 130 degrees. Certainly this is normal sinus rhythm and there is a normal PR interval. In the precordial leads, there is extreme clockwise rotation with the transition zone out in V5 with diphasic waves in leads 2, 3, and AVF, and inversion of the T waves in leads V5 and V6. There is sagging of the ST segments in leads 2 and 3, suggestive, perhaps, of digitalis effect. Also, the diaphasic T waves in leads V1 and V2 suggest right atrial enlargement, and only the R wave present in V3R and the predominant R wave in V1, in the presence of small QRS complexes, suggests right ventricular hypertrophy.

Because of the striking findings on the electrocardiogram, indicating right axis deviation, and a roentgenogram that is compatible with right ventricular hypertrophy and an enlarged pulmonary artery segment, some mention of *pulmonary arterial hypertension* might lead us further toward the diagnosis. However, upon further consideration, primary pulmonary hypertension, thrombosis of major pulmonary vessels, and multiple pulmonary emboli as causes of this illness can be excluded.

Congenital heart disease in some cases can show changes similar to those seen in the roentgenograms and the electrocardiogram, but I shall completely disregard this diagnosis because no murmur is present. Cor pulmonale might be considered, but not that associated with chronic obstructive lung disease, since there is no evidence for this.

Lastly, *valvular heart disease* should be mentioned here. We think of valvular disease as being accompanied by murmurs, but despite the absence of a murmur in this case we should think of mitral stenosis, as Doctor Pudvan suggested when he examined the roentgenograms, even though there is no evidence of left atrial enlargement. The patient did have pulmonary venous hypertension, right ventricular enlargement, and possibly pulmonary arterial hypertension. I think the question then to be asked is: "How could this patient have such a lesion in the absence of a documented murmur?" This could be an instance of what has been called "silent" mitral stenosis even though I am well aware of the fact that most of the cases in this category are due to incomplete auscultation. Those who believe that there are some cases of true silent mitral stenosis think that this aberration is related to severe pulmonary arterial hypertension with resultant low cardiac output. This patient had a low blood pressure in the range of 90/60 mm Hg. Her symptoms could be consistent with a diagnosis of mitral stenosis, even though she did not have orthopnea and hemoptysis. The possible mechanism of silent mitral stenosis is its association with massive thrombi in the left atrium; however, in this instance, atrial fibrillation is almost always present.

Another cause of left ventricular inflow obstruction should be considered—

primary cardiac tumors. Three fourths of these tumors are benign; and of the benign tumors, the majority are myxomas located in the left atrium. With myxoma of the left atrium, the clinical course is shorter and develops more rapidly than that of mitral stenosis. There is usually evidence of arterial emboli, though the incidence of atrial fibrillation is lower than that seen with stenosis. However, even with myxoma, a murmur should be present. It is possible that at the time of examination, the tumor was not in a position to obstruct the valve, and the murmur was missed. In conclusion, *silent mitral stenosis with severe pulmonary arterial hypertension,* and *myxoma of the left atrium,* should be considered the two best possibilities.

Doctor Nickerson's Diagnosis:

(1) Rheumatic heart disease with mitral stenosis, severe pulmonary hypertension, cardiac enlargement, congestive heart failure.

(2) Myxoma of left atrium.

Leonard L. Lovshin, M.D.*:

Thank you, Doctor Nickerson, for an excellent discussion. This was a patient of William L. Proudfit, M.D. I shall now call upon him to make a few comments and to offer his own clinical diagnosis.

William L. Proudfit, M.D.†:

There are some points that were not completely brought out in the protocol, and therefore Doctor Nickerson didn't have a chance to be benefited by this knowledge—or be confused by it. First of all, the disease progressed rapidly. This woman was referred to us with the diagnosis of mitral stenosis, and, ordinarily, patients with this condition do not decline so fast. This immediately made us suspect that mitral stenosis was not the cause of the illness. In addition, this woman was extremely weak and had lost a good deal of weight; neither of these is characteristic of mitral valvular disease. On examination, there were several unusual findings. The mitral first sound was accentuated; this would not be unusual in mitral stenosis, but she had no mitral diastolic murmur. She also had another unusual finding; the protodiastolic sound could be heard clearly in the back. I can't say that I ordinarily listen for protodiastolic sounds in the back, and this, I must admit, confused me somewhat. Previously I have heard loud sounds in this region, but only in patients who have had myxoma of the left atrium. This sound appeared too late in the cycle for myxoma of the left atrium, since it occurred 0.16 second after the second heart sound. Perhaps more emphasis should have been placed on the urinary changes. She did have an abnormal urine; there were an increased number of erythrocytes and 2+ protein even when she was not in congestive failure. As the workup progressed, we narrowed the possibilities to constrictive pericarditis, primary or secondary myocardial disease, or myxoma of the left atrium. I believed that both myxoma and constrictive pericarditis could be excluded because the sound occurred so late and that therefore we were hearing a protodiastolic gallop rhythm. This left us with a diagnosis of *myocardial disease.*

Doctor Proudfit's Diagnosis:

Primary or secondary myocardopathy.

Doctor Lovshin:

We shall now hear from Lawrence J. McCormack, M.D., who will give us the diagnosis based on myocardial biopsy and autopsy findings.

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Lawrence J. McCormack, M.D.*:

Microscopic study of myocardium from the left ventricle and left atrium obtained at the time of surgery showed severe amyloidosis. At the time of autopsy the heart weighed 500 g; there was dilatation of the left atrium and right ventricle, accompanied by moderate hypertrophy. There was only slight hypertrophy of the left ventricle, but no dilatation. The coronary arteries were normal; there was no evidence of pericarditis.

Microscopic examination disclosed heavy deposition of amyloid in the myocardium and surrounding the blood vessels. Study of special sections showed deposits in the sinus node and atrioventricular bundles.

The problem of pulmonary hypertension can be explained by the fact that the lungs were severely and diffusely involved. Amyloid was also demonstrated, in lesser amounts, in the spleen, liver, pancreas, kidneys, and bowel.

The cause of the severe oliguria that occurred after the operation is not entirely clear, since the kidneys were not greatly affected by amyloid. Incidentally, there was a small renal stone that was of no clinical significance.

Anatomic Diagnosis:

Disseminated primary amyloidosis, and cardiomegaly (500 g) due chiefly to hypertrophy and dilatation of the right ventricle and left atrium.

Discussion

Doctor Lovshin:

I should like to state that Doctor Proudfit suggested the possibility of amyloidosis at the time of his initial examination, and he noted this in the record. Since he did not mention this in today's discussion, I assume that he either is overly modest or is somewhat forgetful.

This patient was studied in the cardiac laboratory by William C. Sheldon, M.D., of the Department of Cardiovascular Disease and Cardiac Laboratory, and some valuable information was obtained. The conclusion of his report read as follows:

> "Restrictive cardiopathy with impaired ventricular filling and secondary left atrial and pulmonary hypertension of moderately severe degree. Suspect this is primary myocardial disease. Primary amyloidosis? Cannot exclude constrictive pericarditis."

I should like to know what findings at the time of catheterization of the heart suggest possible primary myocardial disease.

Doctor Sheldon:

I shall try to point out some of those features. When we saw the patient the biopsy had not yet been done and the diagnosis was in doubt. We were faced with the problem of a patient with signs of pulmonary hypertension and a history of symptoms consistent with cardiac failure. We performed complete right- and left-sided heart catheterization studies, and the first thing we discovered was elevation of all of the intracardiac pressures. The patient did, indeed, have moderate pulmonary hypertension, but she also had elevation of the end-diastolic pressure in the left ventricle and significant elevation of the left atrial pressures. In recording a continuous tracing from the left atrium to the left ventricle there was no gradient during diastole.

One of the interesting findings during catheterization was the contour of

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the pressure tracing in the right ventricle, which showed an early diastolic dip with a late diastolic plateau. This is commonly seen in various types of extrinsic restriction of diastolic filling and can be due either to pericardial or to myocardial disease, or, in some cases, to extreme myocardial hypertrophy. Therefore we tried to solve the problem with some motion pictures (could you show the film please?).

One of the considerations, in view of the right axis deviation on the electrocardiogram, was the possibility of primary pulmonary hypertension or multiple pulmonary emboli. The first injection of contrast medium was into the main pulmonary artery, and this shows the main pulmonary artery in the frontal projection. You will notice that there is the normal rapid-velocity flow through the pulmonary circulation, and the total venous drainage from the lungs is directed to the left atrium, which is seen here in the frontal projection. The left atrium is perhaps slightly enlarged. When one looks carefully at the primary, secondary, and even some of the tertiary pulmonary arterial branches, they appear perfectly normal in caliber. We cannot identify a localized or diffuse obstructive process that might indicate multiple pulmonary emboli, nor can we see the secondary changes that occur in patients with primary pulmonary hypertension. This particular injection also served to exclude the presence of anomalous drainage of the pulmonary veins. It also excludes a left-to-right shunt at the atrial level, since demonstration of the left atrium is quite good.

This selective opacification of the left atrium shows it to be definitely enlarged. The catheter has been placed retrograde across the mitral valve and we can see no filling defect, mass, or tumor within the left atrium. You will remember that the patient had sinus rhythm; despite this, there is extremely poor amplitude of the atrial contractions.

This view shows the left ventricle in the right anterior oblique projection; it is not the dilated chamber we might have expected to see. The diastolic size is quite normal. In motion study during diastole there seemed to be a rather thick zone of myocardium between the cavity and the external surface. This frame shows the chamber at the peak of systole, and the end-systolic volume is minimally increased. The striking thing is that, during diastole, the chamber reaches a maximal end-diastolic size and then fails to expand further as the atrium expels its contents. The ventriculogram suggests restricted diastolic filling of the left ventricle.

Because we also had to be completely sure that the patient did not have some unusual form of coronary artery disease, we opacified the coronary arteries and saw that both the right and the left vessels were normal. There was a dominant right coronary artery pattern with no evident atherosclerotic changes.

On the basis of these studies we showed that there was restricted diastolic filling both of the left and of the right ventricles, secondary hypertension and enlargement of the left atrium, secondary pulmonary hypertension, and right ventricular hypertension. The pictures did not suggest the usual hypertrophic process so often seen in idiopathic hypertrophic subaortic stenosis. Therefore the restricted diastolic filling could be due to a myocardial infiltrative process, or it could also be due to an extramyocardial condition such as thickened pericardium. We did attempt to demonstrate the width of the right atrial wall; it appeared to be somewhat thicker than usual, and we could not exclude the possibility of pericardial thickening.

Some of our findings were identical with those seen in other patients with primary amyloid disease affecting the heart. One is the relatively small size of the ventricular chambers, as compared to other forms of primary cardiomyopathies of the nonhypertrophic type. These usually show severe dilatation of the ventricles. Another feature is that during diastole the maximal ventricular size is achieved very early. As diastolic filling continues, and during atrial injection in the presystolic phase of the heart cycle, there is little further expansion of the left ventricle. These findings all indicate a restrictive process, but they do not tell us whether this restriction is in or around the myocardium.

Doctor Lovshin:

Apparently this was the definitive study that led to the decision in favor of thoracotomy for pericardial exploration and myocardial biopsy. I shall now call on our distinguished Visiting Professor of Medicine, W. Proctor Harvey, M.D.

W. Proctor Harvey, M.D.*:

This is a very interesting case. In looking back on the electrocardiograms I don't remember the low voltage that has previously been reported to be common in patients with cardiac amyloidosis. This may be a valuable clinical clue in differentiating the condition of a patient of this type from some other form of cardiomyopathy, especially since many of the other findings can be identical. It would be very unusual for patients with myocardial disease not to have an atrial sound; this finding has been extremely common in our own group of patients. I think this has been a most instructive case and the presentation excellent.

Doctor Lovshin:

Are there any questions?

Nelson G. Richards, M.D.†:

There's just one question I should like to raise here. The patient's chief complaint was that of a myopathy. Among persons who have cardiac disease how often do you find that they complain of inability to comb their hair or lift their arms above their heads unless it be a diffuse disease involving the rest of the body as well as the heart?

Doctor Proudfit:

Difficulty in lifting the arms is not unusual in heart disease, because periarthritis of the shoulders is so common in coronary disease. Since a neurologist is asking the question, I assume he is referring to something else. General weakness is characteristic in patients who have congestive heart failure, and sometimes you do see patients with this condition who have difficulty combing their hair. I do admit, however, that this woman's weakness was out of proportion to other manifestations of the heart disease.

Doctor Lovshin:

Doctor Richards, I think Doctor Proudfit is admitting in a roundabout way that the patient's severe weakness in the arms was due to myopathy, and that the cardiologists could have paid more attention to it. I have no doubt that if this patient had been seen originally in the Department of

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Neurology, you would have arrived at the same diagnosis—and perhaps more easily!

Anita M. Klein, M.D.*:

Was there any evidence of myopathy in skeletal muscle at the time of autopsy?

Doctor McCormack:

Unfortunately we did not examine a specimen of skeletal muscle. Apparently, everyone was too interested in the myocardium. However, this is a pertinent question, because in amyloid disease, functional deficit does not necessarily correlate with the amount of abnormal material seen microscopically. In the kidney, for example, you may find only minute amounts of amyloid in the renal glomeruli, and yet significant proteinuria may occur. In muscle you may find only a small amount of amyloid ringing the blood vessels even though there had been profound weakness. The explanation for this is not yet available. When you suspect amyloid disease and you send in a biopsy specimen, please warn us, because many times the amyloid can be demonstrated only with special stains, and we will not see anything in the routine hematoxylineosin preparations. If the biopsy specimen is a piece of myocardium, we need no advance warning, because all such material is routinely screened for amyloid.

Doctor Harvey:

I should like quickly to make a point. The incidence of amyloid disease is increasing as people live longer. In recent years, more and more cases are being documented in the medical literature, many of them from the older age groups.

Doctor Nickerson:

I should like to ask Doctor Proudfit how he explains the very loud diastolic gallop?

Doctor Proudfit:

Loud ventricular gallops are common in patients who have amyloid or other primary myocardial disease. In contrast to other types of heart disease, these gallops are apt to remain loud when the rate is slowed as a result of adequate treatment for congestive heart failure. Thus, even when congestive failure disappears and the clinical manifestations improve, this auscultatory sign characteristically remains strong. I still don't know why the gallop was heard over the back.

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My husband, a lawyer, often refuses to accompany me to parties because so many people spoil his evening by asking him for advice. I asked a doctor if this happened to him. "All the time!" he said.

"Then how do you get rid of these people?"

"I have a wonderful remedy," the doctor grinned. "When someone begins telling me his ailments, I stop him with one word, 'Undress!' "*

*Jacob Braude: Speaker's Encyclopedia.

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Renal Arterial Disease and Hypertension

An Analysis of Selective Renal Arteriography
in 1500 Consecutive Patients

INCREASING EXPERIENCE with renal arteriography has shown that a variety of changes may be observed in patients with renal arterial disease, and accumulation of data from pathologic studies of diseased renal arteries has indicated that several disease processes may affect the renal arteries.

The arteriographic appearance of the most common renal artery lesion, atherosclerosis, is well recognized. Differing arteriographic finding have appeared in the non-atherosclerotic diseases. Despite dissimilarity in the histologic characteristics, these non-atherosclerotic lesions have been indiscriminately grouped under the term fibromuscular hyperplasia.

In a retrospective correlative analysis of autopsy and surgical specimens of renal arteries with renal arteriograms, McCormack and Associates[1] have shown that the various renal arterial diseases usually have characteristic arteriographic features, so that, when a sufficient length of renal artery is affected, the pathology of the disease process may be predicted from the arteriogram. However, the relative frequency of the various renal arterial diseases in this retrospective study was influenced by the fact that most of the material was obtained from patients who were considered candidates for surgical treatment of renal arterial disease which might be responsible for their hypertension. In addition, accumulation of sufficient pathologic material for study required that many of the arteriograms used in the correlative analysis were derived from the period when translumbar aortography was the primary arteriographic method for study. Dilution of contrast material by aortic blood and overlap of renal arteries by filling of extrarenal arteries, the two major disadvantages of aortographic techniques, often precluded complete and accurate delineation of the entire renal arterial system of both kidneys.

The present study is an analysis of renal arterial disease in 1500 consecutive hypertensive patients studied by selective renal arteriography. Its purpose is to define the incidence, type and distribution of the various categories of renal arterial disease in a large group of selected hypertensive patients. Included are the findings in 100 patients, previously reported.[2]

Materials and Methods

One thousand five hundred hypertensive patients who were studied consecutively were selected, usually on the basis of the following clinical criteria: Onset of hypertension below age 40; documented recent onset of hypertension in all groups; exacerbation or acceleration of existing hypertension or an abdominal bruit in association with hypertension. Some were selected because of disparity in renal sizes, nonfunctioning of a kidney or difference in renal function demonstrated by intravenous urography.

Renal arteriography was performed in the majority of the patients by the Seldinger technique[3] of percutaneous femoral catheterization. In some patients with aorto-iliac occlusions, the catheter was introduced by open brachial arteriotomy. A pre-moulded Odman-Ledin catheter* of medium size (green) was used in most studies. Using image intensification fluoros-

*A.B. Kifa Co., Stockholm.

copy, selective renal arteriography was carried out using 4 to 8 cc of contrast material (Hypaque 50%). In all patients, aortography was performed by pressure injection of 20 to 40 cc of contrast material (Hypaque 75%).

Radiographs following selective injections were obtained in anteroposterior and posterior oblique projections and aortographic films in the anteroposterior projection. As individual circumstances warranted, aortograms were also obtained in the erect or oblique projections.

Arterial diseases were categorized using the criteria of McCormack et al.[1] Lesions were classified according to their primary location in the vessel wall. There are two that primarily affect the intima: atherosclerosis and intimal fibroplasia. Three types predominantly involve the media: medial fibroplasia with aneurysm, fibromuscular hyperplasia and subadventitial fibroplasia. Using the arteriographic criteria which have been set forth in this classification, we have been unable to differentiate consistently fibromuscular hyperplasia from intimal fibrosis. Accordingly, in the present study, these two types of diseases have been grouped.

A category of fibrous disease of undetermined type has been included because either the features were not sufficiently characteristic or the length of the artery affected was too short for the manifestations of the particular type of arterial disease to be discerned.

Results

Of the 1500 patients studied, renal arterial disease of varying severity and type was demonstrated in 649 (43.3 percent) patients and classified into groups on the basis of the arteriographic characteristics: atherosclerosis, fibrous disease, a combination of atherosclerosis and fibrous disease, renal artery aneurysms, renal artery aneurysms associated with atherosclerosis, and a miscellaneous category including embolic and thrombolic disease and complete occlusion of the renal artery (Table 1).

Atherosclerotic Renal Artery Disease

Atherosclerotic disease of the renal arteries was observed in 62 percent of the patients with arterial disease (Figure 1). Of these patients, 65.2 percent were males. The majority of the patients, 87.5 percent, were in the fifth, sixth or seventh decades of life (Table 2). Stenosis was estimated to be less than 50 percent in 64.6 percent of the patients, while 35.4 percent had lesions of greater severity. Bilateral disease was present in 34.9 percent of the patients, and in those patients with unilateral disease, there was no difference in the frequency of right and left-sided involvement. Lesions of the orifice and proximal centimeter of the renal artery were found in 58 percent of the patients, of distal main renal artery disease in 24 percent, and of interlobar branches alone or in association with main renal artery disease, in 18 percent. One fourth of the patients with lesions less than 50 percent occlusive had disparity in renal lengths of 1.0 cm or more as measured on the intravenous urogram. The incidence of disparity in lengths was 56

TABLE 1

Type of Lesion and Degree of Occlusion—Patients and Percentages ( )

		Disease < 50% Occlusive	Disease > 50% Occlusive
Atherosclerosis	404(62.3)	261 (64.6)	143 (35.4)
Fibrous Disease Only	179(27.5)	118 (65.9)	61 (34.1)
Atherosclerosis and Fibrous Disease	14(2.2)	7 (50.0)	7 (50.0)
Aneurysm	25(3.9)	25 (100.0)	0 (0)
Aneurysm and Atherosclerosis	15(2.3)	15 (100.0)	0 (0)
Embolus, Thrombosis, Complete Occlusion	12(1.8)	1 (8.4)	11 (91.6)
TOTALS	649(43.3)	427	222
NORMAL	851(56.7)		



Fig. 1—Typical appearance of eccentric atherosclerotic lesion located in the proximal portion of the right renal artery and associated with moderate post-stenotic dilatation.



Fig. 2—Medial fibroplasia involving the main renal artery to the bifurcation showing the typical "beaded" appearance.



Fig. 3—Subadventitial fibroplasia involving the distal renal artery, showing a severe stenosis and the presence of abundant collateral circulation.



Fig. 4—Intimal fibroplasia involving the main renal artery and extending to the region of the major bifurcation associated with a dissecting aneurysm of the main renal artery.

percent in those patients with lesions of greater severity.

Non-Atherosclerotic Renal Artery Disease

One hundred ninety-three patients had non-atherosclerotic disease as judged by the arteriographic appearance. Of these, 88.6 percent had fibrous disease alone and the remaining, fibrous disease in combination with atherosclerosis.

One hundred forty-nine patients (77.2 percent) had lesions classified as medial fibroplasia; 16 (8.3 percent), subadventitial fibroplasia; and 17 (8.8 percent), either fibromuscular hyperplasia or intimal fibrosis (Table 3 and Figures 2, 3 and 4). In 10 patients (5.2 percent) the disease did not appear to be atherosclerotic but was not characteristic of any of the fibrous diseases classified above. One patient, age 18 years, who received radiation therapy to the retroperitoneum at 18 months of age, following surgical resection of a Wilms' tumor, was found to have severe fibrotic disease of the aorta and the two renal arteries supplying the remaining kidney when the patient was re-examined because of hypertension at the age of 18 years.

Excluding those patients who had both fibrous and atherosclerotic lesions, 80.4 percent of the patients were females. At the time of arteriography, the majority of these patients were in the fifth decade (48.0 percent) with the fourth and sixth decades being next in frequency (20.1 percent and 15.1 percent respectively). See Table 2.

Two thirds of the patients were judged to have lesions less than 50 percent occlusive. Involvement of the renal artery distal to its first centimeter was found in 95 percent of the patients. Of these, 35 percent affected only the main renal artery, 47 percent the main artery and branches, and branch involvement only in 13 percent.

Almost half of the patients (45.2 percent) had bilateral disease. Unilateral involvement was considerably more frequent on the right, being observed in 80 of the 98 patients (81.6 percent).

Bilateral renal artery involvement was present in 48.8 percent of patients with medial fibroplasia. Of the remaining patients with unilateral involvement, 85.5 percent had right-sided involvement. Bilateral disease was present in 25 percent of the patients with subadventitial fibroplasia, and of those with unilateral disease, three-quarters had right renal artery disease.

There were 17 patients categorized arteriographically as having either fibromuscular hyperplasia or intimal fibrosis. Of these, six had bilateral disease, and eight of the eleven with unilateral disease had right renal artery involvement.

Considering the fibrous diseases collectively,

TABLE 3

Type and Incidence of Fibrous Disease
Patients and Percentage

Medial fibroplasia alone	135	
Medial fibroplasia associated with atherosclerosis	14	149 (77.2%)
Subadventitial fibrosis		16 (8.3%)
Fibromuscular hyperplasia or intimal fibrosis		17 (8.8%)
Radiation fibrosis		1 (0.5%)
Unclassified		10 (5.2%)
		193 (100 %)

TABLE 2

Atherosclerosis and Fibrous Disease (Combined Lesions Excluded)
Type of Disease, Age and Sex of Patients, Numbers and Percentages ( )

Age	Athero-sclerosis	Male	Female	Fibrous Disease	Male	Female
0-9	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
10-19	1 (.3)	1 (100.0)	0 (0)	4 (2.2)	3 (75.0)	1 (25 0)
20-29	6 (1.4)	3 (50.0)	3 (50.0)	14 (7.8)	4 (28.6)	10 (71.4)
30-39	29 (7.2)	20 (69 0)	9 (31.0)	36 (20.1)	7 (19.4)	29 (80.6)
40-49	119 (29.5)	82 (68.9)	37 (31.1)	86 (48.0)	11 (12.6)	75 (87.4)
50-59	138 (34.2)	83 (60.1)	55 (39.9)	27 (15.1)	7 (25 9)	20 (74.1)
60-69	97 (23.8)	65 (66.7)	32 (33.3)	11 (6.2)	3 (22.3)	8 (77.7)
70-79	14 (3.5)	10 (71.4)	4 (28.6)	1 (.6)	0 (0)	1 (100.0)
	404 (100.0)	264 (65.2)	140 (34.8)	179 (100.0)	35 (19.6)	144 (80.4)

one third of the patients with lesions less than 50 percent occlusive, had a difference in renal size as determined by measurement of renal length. One half of patients with lesions more than 50 percent occlusive had disparity in renal size.

Other Lesions

Coexistence of atherosclerosis and medial fibroplasia was found in 14 patients and the frequency of the more stenotic lesions was higher than in those patients with either atherosclerosis or medial fibroplasia alone.

Aneurysms with or without other lesions of atherosclerosis were present in 40 patients, and there was no predilection for involvement of either side. All were located in the distal renal artery and most originated from interlobar branches.

In a miscellaneous category were 12 patients who had emboli or thrombosis of a branch or complete occlusion of the main artery, the latter without features which would allow diagnosis of the type of disease which produced the thrombosis.

The occurrence of single and multiple renal arteries was considered with reference to the presence of renal arterial disease. Thirty-five percent of the patients without renal arterial disease had multiple renal arteries as compared with 32 percent of the hypertensive patients with renal artery disease. This incidence was similar to a control group of 390 normotensive patients in which 32 percent had multiple renal arteries.

The presence of multiple renal arteries was also considered with reference to the various types of lesions which were demonstrated. The findings (Table 4) showed no significant variation in the various categories, with the exception of the miscellaneous category in which there were only 12 patients. Further, there was no trend toward multiple renal arteries in the four types of fibrous disease (Table 5). The higher incidence of single renal arteries in patients with subadventitial fibrosis is not significant because of the small group and the higher incidence of solitary kidneys.

Discussion

The true incidence of renal arterial disease in hypertensive patients is difficult to determine. While some degree of selection of patient material can be eliminated by examination of necropsy material, this type of examination

TABLE 4

Type of Renal Artery Disease Correlated with Single and Multiple Renal Arteries

	Single Renal Artery	Multiple Renal Arteries	Absent Kidney	Total
Atherosclerosis	256 (63.4%)	136 (33.7%)	12 (2.9%)	404 (62.3%)
Fibrous Disease	119 (66.5%)	52 (29.1%)	8 (4.4%)	179 (27.5%)
Atherosclerosis & Fibrous Disease	7 (50.0%)	4 (28.6%)	3 (21.4%)	14 (2.2%)
Aneurysm	16 (64.0%)	9 (36.0%)	0 (0)	25 (3.9%)
Aneurysm and Atherosclerosis	10 (66.7%)	5 (33.3%)	0 (0)	15 (2.3%)
Emboli, Thrombosis, Complete Occlusion	8 (66.7%)	1 (8.3%)	3 (25.0%)	12 (1.8%)
				649 (100.0%)

TABLE 5

Type of Fibrous Disease Correlated with Single and Multiple Renal Arteries

	Single Renal Artery	Multiple Renal Arteries	Absent Kidney	Total
Medial Fibroplasia	100 (67.1%)	43 (28.9%)	6 (4.0%)	149
Subadventitial Fibrosis	11 (68.8%)	2 (12.5%)	3 (18.7%)	16
Fibromuscular Hyperplasia or Intimal Fibrosis or Uncertain Type	15 (55.6%)	10 (37.0%)	2 (7.4%)	27
Radiation Fibrosis			1 (100.0%)	1
				193

does not lend itself well to determination of the extent of renal arterial disease. Varying degrees of patient selection for renal arteriography certainly tend to influence the incidence of disease. As indicated earlier, patients in the present series were chosen because of the presence of "inappropriate" hypertension or because of abnormalities on the intravenous pyelogram. The incidence of renal arterial disease of 43.3 percent in this series is approximately the same (52 percent) as reported earlier in a group of 100 relatively unselected patients.[2] Both of these figures are higher than previously reported from this institution. In 1959 and 1961,[4,5] 28 percent of the patients in whom translumbar aortograms were done were found to have arterial disease. Another feature which distinguishes the present series from earlier reports is the greater frequency of branch arterial disease. Lesions of the primary renal arterial branches were encountered in 15.4 percent of the patients who had atherosclerosis and 57.6 percent of the patients with fibrous disease of the renal artery. The difference is presumably due to improved visualization of arterial branches made possible by the selective technique.

While various disease processes which affect the renal artery may produce stenosis, atherosclerotic disease is the most common (62.1 percent). The first reports[6] of the pathology of non-atherosclerotic disease originating from this institution indicated that most disease that was not atherosclerosis represented a type of process in which muscular hypertrophy was prominent, and the name fibromuscular hyperplasia was used to describe this condition. These reports, however, described the findings in a small number of arteries. As experience has increased, it has become apparent that most of the lesions which are not atherosclerotic do not have muscular hyperplasia as a prominent portion of the histologic characteristics, but rather collagen deposition. Classification of non-atherosclerotic disease used in this report takes into consideration a variety of disease processes based upon the predominant microscopic features and the primary location of the lesion in the vessel wall. It is similar to that described by Hunt and associates[7] but has the additional advantage that a rather close arteriographic-pathologic correlation is possible.

As experience has increased, it has also become apparent that the arteriographic features of fibromuscular hyperplasia and intimal fibrosis closely resemble each other and therefore cannot be distinguished. However, the arteriographic appearance of both of these lesions is distinctly different from that of medial fibroplasia and subadventitial fibrosis.

Summary

On the basis of an arteriographic correlation with histologic material, diseases of the renal artery have been divided into those affecting the intima: atherosclerosis and intimal fibroplasia; and those affecting the media: medial fibroplasia, fibromuscular hyperplasia and subadventitial fibrosis. Renal artery disease was encountered in 649 (43.3 percent) of the patients. Of these, 62.1 percent had lesions of the atherosclerotic type and 25.2 percent lesions of the non-atherosclerotic type. Atherosclerotic lesions were predominantly located in the proximal portions of the renal artery and fibrous lesions in the distal renal artery and primary branches. The peak incidence of detection of atherosclerosis was in the fifth, sixth and seventh decades and 65.2 percent of the patients were males. Fifty percent of the patients with fibrous disease were in the fifth decade and 81.8 percent of all patients with fibrous disease were females. Three fourths of patients with fibrous disease had medial fibroplasia. Stenotic disease of more than 50 percent was present in approximately one third of the patients with atherosclerosis and fibrous disease. The frequency of reduction of renal size in the kidney involved with renal arterial disease increased with the severity of the stenosis. However, in both the patients with atherosclerosis and fibrous disease, a significant percentage of patients with stenotic disease more than 50 percent did not have discrepancy in renal size. The incidence of renal arterial disease was the same in patients with single and multiple renal arteries.

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Sources of sinus headache



REGION OF SENSATION

FRONTAL SINUS—headache localized over the frontal region, commonly beginning in the morning. Eyes painful to touch, may be slight swelling over eyes, puffy eyelids.

SPHENOID SINUS—most difficult to diagnose. Headache or sense of pressure over vertex. May be pain in ear or mastoid region.



MAXILLARY SINUS—headache and tenderness under eyes at top of cheekbones, usually starting in early afternoon. Possible swelling of cheek. Pain in jaw and back teeth.

ETHMOID SINUS—headache, tightness in upper part of bridge of nose and well down its sides. Pain, deep-seated behind the eyes and in inner corners of the eyes.



TURBINATES—pain along medial and lateral walls of the inside of the nose. Headache in frontal region, along supraorbital ridge, a feeling of fullness in the head.

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Grand Rounds

Gastrointestinal Causes of Megaloblastic Anemia

SINCE CASTLE and Townsend's[1] experiments showed that the underlying defect in pernicious anemia was a failure of gastric secretion of intrinsic factor, the relationship between gastrointestinal disorders and megaloblastic anemia has been widely studied. Many questions still remain unanswered, but a comprehensive view of this relationship has been established, and it is the object of this paper to review the subject from a clinical standpoint (Table 1).

Lack of vitamin B_{12} (Castle's original "extrinsic factor"), or of folic acid, leads to megaloblastic anemias that are morphologically indistinguishable.

TABLE 1
Gastrointestinal Causes of Megaloblastic Anemia

Causes	Deficiency*	
	B_{12}	Folic acid
I		
Pernicious anemia	+++	0
Total gastrectomy	+++	0
Partial gastrectomy	++	+
II		
Gluten-induced enteropathy	+	++
A. Adult	+	++
B. Juvenile	0	++
Tropical sprue	++	+++
Ileal bypass or resection	+++	0
Regional enteritis		
Ileum	+	0
Jejunum	0	+
III		
Small-bowel diverticula	+++	+
Blind-loop syndrome	+++	+
Diphyllobothrium latum	+++	0

*0 = none, + = mild, ++ = moderate, +++ = severe

However, since these substances are metabolized variously by the gastrointestinal tract, it is sometimes possible to infer from the clinical picture which substance is likely to be absent. Although in this report we are concerned mainly with megaloblastic anemia, it must be kept in mind that a deficiency of vitamin B_{12} or of folic acid affects many systems in addition to the hematopoietic system.

Man and other higher forms of animal life are unable to synthesize vitamin B_{12} and have to rely on bacteria as the primary source. The vitamin is present in almost all foods of animal origin, and the average American diet provides approximately 15 μg per day, of which about 10 percent is actually absorbed, and this quantity is not much greater than the daily adult requirement of 1 μg. However, dietary deficiency of vitamin B_{12} seldom occurs except in strict vegetarians. This ingested vitamin B_{12} combines with the intrinsic factor secreted by the fundus of the stomach, possibly by the parietal cells.[2] The exact nature of the reaction between the intrinsic factor and vitamin B_{12} is not known. However, there is no doubt that lack of the intrinsic factor leads to failure to absorb vitamin B_{12}.

Another unique feature of vitamin B_{12} digestion is that the vitamin is absorbed almost exclusively in the terminal few feet of the ileum.[3,4] The absorption of a molecule as large as vitamin B_{12} almost certainly involves a specific mechanism.[5] Although the exact nature of this mechanism is not clearly understood, pinocytosis at specific absorption sites in the ileum is probably involved.[6] Evidence indicates that vitamin B_{12} is separated from the intrinsic factor before being absorbed; but the suggestion that a "releasing factor" may be involved[7,8] has not been confirmed. When vitamin B_{12} is ingested in large amounts, absorption can take place in the upper jejunum by means of mass action, thus bypassing the intrinsic factor mechanism.[5] The total body stores of vitamin B_{12} amount to from 1 to 2 g.[9] On the basis of a daily absorption of 1 μg,[10] it may be calculated that it can take as long as seven years to exhaust the body stores if absorption were to cease entirely.

From this brief outline, a broad etiologic classification of gastrointestinal causes of vitamin B_{12} deficiency can be inferred:

1. Lack of the intrinsic factor.
2. Competition for vitamin B_{12} within the gastrointestinal tract.
3. Failure to absorb vitamin B_{12} because of lesions of the ileum.

The digestion and absorption of folic acid (folate) differ considerably from those of vitamin B_{12}. A normal daily American diet contains approximately 1000 μg of folic acid, from 5 to 10 percent of which is absorbed.[11] This absorption takes place in the proximal jejunum and is probably an active process;[12] however, no mechanism comparable to the vitamin B_{12}-intrinsic factor reaction is involved. Although folic acid is widely distributed among foodstuffs, the body stores may be depleted in from three to six months; thus, dietary deficiency of folic acid is much more common than dietary deficiency of vitamin B_{12}.[13] The relationship between gastrointestinal disease and folic acid deficiency is complicated by the fact that folic acid deficiency itself causes intestinal lesions.[13] Thus it is necessary to include nutritional folic acid deficiency in a classification of gastrointestinal disorders associated with such deficiency. A broad classification of the gastrointestinal disorders associated with folic acid deficiency is as follows:

1. Dietary deficiency of folic acid.
2. Competition for folic acid in the gastrointestinal lumen.
3. Failure to absorb folic acid because of lesions of the small intestine.

Deficiencies of vitamin B_{12} and folic acid not infrequently coexist, particularly when there is either widespread disease of the small intestine, or bacterial competition for the two nutrients.

Clinical Application

A. *Vitamin B_{12} deficiency.*

1. Intrinsic factor deficiency.

a. Addisonian pernicious anemia.

The essential defect in pernicious anemia is the lack of production of the intrinsic factor, associated with atrophic gastritis or gastric atrophy. Failure of the stomach to secrete hydrochloric acid is an almost invariable accompaniment. The gastric lesion is not specific for pernicious anemia, since histologically indistinguishable lesions are not invariably associated with reduced intrinsic factor secretion.[14] Recent evidence suggests that pernicious anemia may be a manifestation of an auto-immune process, possibly on a hereditary basis.[5, 14-16] Parietal cell antibodies have been demonstrated by immunofluorescent technics in the serum of approximately 95 percent of patients with pernicious anemia.[17] Antibodies to intrinsic factor have also been reported; however, these occur in only from 40 to 57 percent of patients.[5,15] The parietal cell antibody is also found in the serum of patients who have atrophic gastritis but who do not have overt pernicious anemia,[14] and it may be possible that this represents a 'preanemic' stage of the disease. These patients do not exhibit the intrinsic factor antibody. It is possible to explain the presence of these antibodies on the basis of the 'hidden-antigen' theory that suggests that damage to the mucosa of the stomach may release antigenic material that is 'foreign' to the antibody-forming tissues and acts as a stimulus to the formation of parietal cells and intrinsic factor antibodies.[11,89] Whether this leads to the development of atrophic gastritis with subsequent intrinsic factor deficiency, or merely perpetuates the gastric lesion, is not known.

The association of pernicious anemia with thyroid disease is well documented. Indeed, parietal cell antibodies have been found in the serum of patients with myxedema and Hashimoto's thyroiditis, and, conversely, thyroid antibodies have been found in the serum of patients with pernicious anemia.[14,15,20,21] There is some histologic similarity among the lesions found in these various diseases, and this fact has been used as further evidence in favor of the theory that they are of an auto-immune origin.[15,22]

Although pernicious anemia seldom occurs under the age of 40 years, it may on a rare occasion occur in childhood. There are two forms of childhood pernicious anemia.[23] In one form, a selective lack of the intrinsic factor secretion exists, unassociated with achlorhydria or any histologic gastric lesion. Parietal cell and intrinsic factor antibodies are not found in this type of anemia, which appears to be an inborn error of metabolism unrelated to addisonian pernicious anemia. The other form of pernicious anemia seen in children is indistinguishable from that seen in adults. There is considerable evidence to suggest that pernicious anemia, gastric atrophy, and gastric carcinoma occur more frequently in patients of blood group A than in those of any other blood group.[24,25]

b. Total gastrectomy

An inevitable sequel to microscopically proved total gastrectomy is a megaloblastic anemia indistinguishable from pernicious anemia, occurring as a result of the removal of the source of the intrinsic factor.[26] This complication develops in from two to seven years postoperatively regardless of the reason for the surgical procedure or the type of reconstruction performed. The interval

corresponds with the time required to exhaust the body stores of vitamin B_{12}.

c. Subtotal gastrectomy

Anemia develops in from 20 to 56 percent of patients who have undergone partial gastrectomy.[27-30] In the majority of patients the anemia is attributable to iron deficiency, but megaloblastic anemia has been reported in increasing numbers after proximal subtotal gastrectomy[27] but in only from 1 to 4 percent of patients who have undergone distal subtotal gastrectomy.[27,30]

Deller and Witts[28] and Pedersen and associates[31] pointed out that examination of the peripheral blood smear may be an unreliable measure of vitamin B_{12} deficiency in the anemia after partial gastrectomy, since the hematologic features of vitamin B_{12} deficiency may be masked by coexisting iron deficiency. Subsequently, Deller and Witts[28] and Hines and associates[30] utilized the more sensitive indices of serum B_{12} and folate levels. These authors found that subnormal levels of serum vitamin B_{12} were more frequently demonstrated after partial gastrectomy for gastric ulcer than for duodenal ulcer. There was no such correlation in the case of folate deficiency. Patients with histologic evidence of chronic diffuse gastritis in the resected segment had a greater incidence of postoperative subnormal levels of serum vitamin B_{12} than did patients with histologically normal gastric mucosa. This difference can be accounted for by a decrease in secretion of the intrinsic factor in the former group. Low serum vitamin B_{12} and folate levels were commonly associated with low serum iron levels. Not surprisingly, iron therapy given to these patients restored the iron content of the bone marrow and increased its megaloblastic features, but failed to correct the anemia. All patients in this series with low serum vitamin B_{12} levels required parenteral administration of vitamin B_{12} in order to achieve normal blood hemoglobin levels.

The pathogenesis of vitamin B_{12} deficiency that may, on rare occasions, develop after partial gastrectomy, appears to be the impairment of secretion of the intrinsic factor.

2. Competition for vitamin B_{12} within the gastrointestinal tract.

Two disorders are within this group: first, the "blind-loop" syndrome in which bacteria in the gastrointestinal tract compete for the available vitamin B_{12}; and secondly, infestation by the fish tapeworm (Diphyllobothrium latum). In both these conditions, absorption of vitamin B_{12} is impaired despite the presence of an adequate amount of the intrinsic factor. Normal absorption of vitamin B_{12} is restored after eradication of the organisms.

a. Blind-loop syndrome

Megaloblastic anemia arising in the blind-loop syndrome is usually due to vitamin B_{12} deficiency. It may be found in patients with surgically formed blind loops after partial gastrectomy of the Polya or of the Billroth II-Hofmeister type, particularly if there is a long afferent loop.[30,32] Diverticula of the jejunum may be associated with megaloblastic anemia and may have been associated with the development of abnormal bacterial flora thought to compete with the host for vitamin B_{12}.[33,34] Strictures of the small intestine, internal fistulas, and other lesions are less common causes of this syndrome.[35,36]

Normally the small intestine is virtually free of bacteria, but when stasis occurs, bacteria are able to proliferate.[37,38] Thus, intestinal stasis is the hallmark of this syndrome, although other factors such as impaired blood flow to the intestine may play a part in permitting growth of organisms. The coliform group of organisms is most frequently found in the stagnant region.[39] Although steatorrhea may on occasions be associated with the blind-loop syn-

drome, there is little doubt that the vitamin B_{12} lack results from competition for the vitamin or its inhibition by the organisms themselves. This reduces the quantity of vitamin B_{12} which reaches the distal ileum, and hence the amount available for absorption. Although the competition theory has received the widest attention, other etiologic factors may be involved. These include the possibility that "toxic" substances elaborated by bacteria or other organisms may interfere with vitamin B_{12} absorption, and that by altering the pH in the jejunum these organisms may render unstable the vitamin B_{12}-intrinsic factor complex.[33] Treatment with oral broad-spectrum antibiotics will correct the deficiency,[30,33,36,37,39] a fact that lends weight to the theory of bacterial competition.

b. Diphyllobothrium latum infestation

Megaloblastic anemia due to the fish tapeworm is rare in the United States. However, occasional cases have been reported from the Great Lakes region. In Finland it has been estimated that 20 percent of the population harbors the organism, and, of these, megaloblastic anemia develops in from 1 to 3 percent.[40] Megaloblastic anemia occurs only when there is massive infestation of the proximal portions of the small intestine.[41] Uptake of vitamin B_{12} by the parasite has been found, and the anemia is apparently due to competition with the host for the available vitamin B_{12}.

3. Failure to absorb vitamin B_{11} due to lesions of the mucosa of the small intestine.

a. Tropical sprue

Tropical sprue, a malabsorptive disease affecting the entire small bowel, is endemic to the Caribbean countries, the Indian subcontinent, and southeast Asia. Megaloblastic anemia may be found in as many as 72 percent of patients in the advanced stages of the disease.[42] The reported incidence of megaloblastic anemia due to vitamin B_{12} deficiency ranges from rare to predominant and it may or may not be associated with folic acid deficiency. These variations appear to be directly related to geographic differences and to the acuteness of the disease.[42-45] Vitamin B_{12} deficiency has been reported to be the predominant cause of megaloblastic anemia in patients with tropical sprue in Haiti, but a rare cause in patients with acute tropical sprue in Singapore. The mechanism of vitamin B_{12} malabsorption is not clearly understood, but it is perhaps related to villous atrophy that involves the mucosa of the entire small bowel, including the ileum.[46,47] In therapy, pharmacologic doses of vitamin B_{12} or of folic acid, or the administration of tetracycline, will usually induce clinical remission and increase intestinal absorption of the nutrient agents.[42,46,48-50]

b. Gluten-induced enteropathy

Gluten-induced enteropathy, like tropical sprue, is a disease of the small-bowel mucosa, characterized by villous atrophy related to an intolerance to gluten in the diet.[51] Megaloblastic anemia due to vitamin B_{12} deficiency is an infrequent complication of this condition among adults. However, decreased serum vitamin B_{12} levels are not unusual.[52,53] No abnormality of the intrinsic factor secretion has been found, and vitamin B_{12} absorption returns to normal when gluten is removed from the diet. Serum vitamin B_{12} levels are generally normal among children with this disease, and the cause of megaloblastic anemia in the juvenile form is usually related to folic acid deficiency.[54]

Recent studies[55-57] have shown that severe vitamin B_{12} deficiency affects the epithelium of the small intestine, with resultant mucosal changes, which are thought to be the result of long-standing vitamin B_{12} deficiency

and not the cause of a vitamin B_{12} absorptive defect.

c. Regional enteritis

The most common cause of specifically impaired absorption of vitamin B_{12} is regional enteritis with involvement of the terminal ileum.[12,58] However, megaloblastic anemia becomes a virtual certainty when extensive resection of the ileum has been performed.[3,59]

d. Small-bowel resection

Decreased absorption of vitamin B_{12} occurs after resection or after bypass reconstruction of the distal ileum.[3,60] Vitamin B_{12} deficiency invariably develops when more than six to eight feet of terminal ileum is resected or bypassed.[3] Megaloblastic anemia and other manifestations of vitamin B_{12} deficiency occur from one and one-half to six years after operation, and appear to be directly related to loss of the absorptive site of vitamin B_{12}.

B. *Folic acid (folate) deficiency*

Megaloblastic anemia due to folate deficiency may be caused by gastrointestinal disorders that affect the jejunum, as well as by nutritional or dietary lack. Folic acid is absorbed primarily in the jejunum, and it appears that the major mechanisms in folic acid deficiency are malabsorption due to abnormal jejunal mucosa, or dietary lack. Additionally, there are mechanisms of folic acid deficiency which are poorly understood, such as that occurring in late pregnancy,[61] and that associated with anticonvulsive drug therapy.[62,63] In the former instance, a conditioned lack may result from preferential fetal uptake of folic acid in a mother whose intake is borderline. In the latter instance it is postulated that there is competition or inhibition of folic acid.

1. Nutritional or dietary lack.

Folic acid deficiency with resultant megaloblastic anemia may occur in almost any form of severe nutritional deficiency, and it is particularly common in the nutritional deficit associated with alcoholic cirrhosis of the liver.[64,65]

2. Failure to absorb folic acid because of lesions of the small intestine.

a. Partial gastrectomy

Megaloblastic anemia due to folic acid deficiency resulting from partial gastrectomy has been reported only rarely.[29,30,66,67] Anemia associated with combined iron and folic acid deficiency (on the basis of bypass of the proximal jejunum or rapid passage of foodstuff through the absorptive area) and normal serum vitamin B_{12} levels is a more common finding.[30] This anemia may demonstrate morphologic characteristics both of iron deficiency and of folic acid deficiency ("dimorphic" anemia) with resultant hypochromic microcytic cells in association with macrocytic erythrocytes and a megaloblastic bone marrow. Iron therapy alone will often afford temporary alleviation of the anemia, but the morphologic picture of folic acid deficiency and low serum folate levels remains.[30] The pathogenesis of folic acid deficiency after partial gastrectomy is not clear; poor dietary intake may sometimes be the cause. There also seems to be a relationship between iron deficiency and folic acid deficiency, perhaps related to jejunal malabsorption of both of these nutrient agents.

b. Tropical sprue.

The incidence of megaloblastic anemia secondary to folic acid deficiency may be quite high in tropical sprue, and in the acute form of the disease folic acid deficiency appears to be the primary cause.[42,43] Although the mucosal abnormality is presumably related to the malabsorption of folic acid, the

exact nature of the defect is not known.[47] Involvement of the ileal mucosa may account for vitamin B_{12} malabsorption. Since the intestinal lesions and the low serum folate levels respond to oral tetracycline therapy, the belief is no longer held that folic acid deficiency is itself the cause of tropical sprue.[46,47,50]

c. Gluten-induced enteropathy.

Folic acid absorption may be severely depressed in gluten-induced enteropathy, because of the jejunal abnormality, and folic acid deficiency is the most common cause of megaloblastic anemia in the adult form of this disease.[52] Although serum vitamin B_{12} levels may be somewhat decreased, overt vitamin B_{12} deficiency is infrequent. In the juvenile form of gluten-induced enteropathy, megaloblastic anemia due to folic acid deficiency is constant, and serum vitamin B_{12} levels are normal.[54] The severity of impairment of folic acid absorption appears to correlate well with the degree of jejunal villous atrophy.[68,69] The return of folic acid absorption to normal levels and the remission of anemia occur with gluten restriction in the diet.[48,52]

d. Blind-loop syndrome.

Folic acid deficiency as the sole cause of megaloblastic anemia is extremely rare in the "blind-loop" syndrome. Folic acid deficiency has been found in association with jejunal diverticulosis (and megaloblastic anemia), but this appears to be a minor contributing factor to the megaloblastic anemia that may be present.

e. Regional enteritis.

Folic acid malabsorption may occur in inflammatory disease of the small intestine, with jejunal involvement, and decreased folate levels may be found in the serum.[12] However, megaloblastic anemia solely due to folate deficiency is rare in regional enteritis, since involvement of the ileum is much more frequent than that of the jejunum.

Summary

Gastrointestinal causes of megaloblastic anemia are deficiencies of absorption of vitamin B_{12} and/or folic acid. Vitamin B_{12} deficiency may result from: failure of secretion of the intrinsic factor; mucosal abnormalities in the terminal ileum which prevent vitamin B_{12} absorption; competition for vitamin B_{12} by organism in the small intestine. Folic acid deficiency may result from dietary lack or mucosal abnormalities of the jejunum which prevent folic acid absorption.

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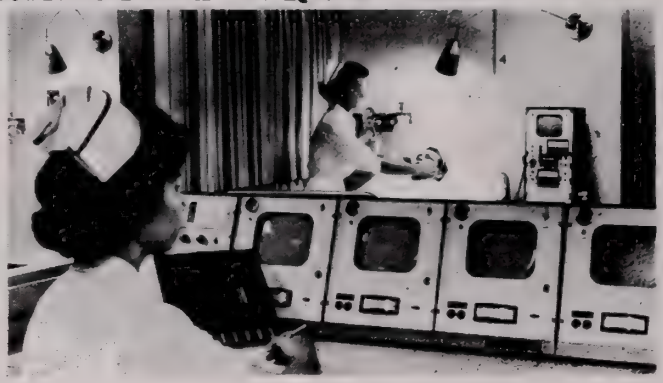
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Techniques

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MANY PATIENTS who are unable to take food orally nevertheless maintain essentially normal intestinal motility and absorption. Conditions that interfere with oral sustenance include neoplasms of the oropharyngeal region, severe maxillofacial trauma, neurologic conditions, and miscellaneous illnesses that depress the appetite and alter the states of consciousness. Methods of sustaining a patient who cannot eat food are by nasogastric intubation, by intravenous feedings, by transperitoneal gastrostomy, and by cervical esophagostomy.

During the last five years at the Cleveland Clinic Hospital, cervical esophagostomy has been created in many patients who require extraoral sustenance for more than a week. This procedure was initially described by Klopp,[1] who performed it for the treatment of obstructive esophageal carcinoma. Ketcham and Smith[2] subsequently demonstrated the effectiveness of the cervical esophagostomy in a large number of patients. Early experience with this procedure at the Cleveland Clinic was reported[3] in 1964. Since that report, feeding cervical esophagostomy has been performed on 86 patients; it has proved beneficial in a great diversity of conditions. The operation has been without significant early or late complications. Anesthesia for this procedure may be either local or general. A brief description of the technic follows.

A nasogastric tube simplifies identification of the esophagus. An incision is made about 3 cm above and parallel to the clavicle (Figure 1A). The sternocleidomastoid muscle is retracted laterally (Figure 1B), and with blunt dissection the thyrolaryngeal structures are separated from those of the carotid sheath. In this fashion the bodies of the lower cervical vertebrae are approached (Figure 1 C), and the esophagus, lying just anterior to them, is gently mobilized (Figure 1 D). Traction sutures secure the esophagus while an opening is made (Figure 1 E). The nasogastric tube is withdrawn from the nose, facilitating passage of a tube through the esophagostomy (Figure 1 F), and the wound is loosely closed with one or two skin sutures. The feeding tube is anchored securely to the skin and serves as a wound drain.

Within one week the esophagostomy tract has become well established, and the tube may be removed and replaced. Rapid obliteration of the tract occurs after removal of the tube.

Comments

Cervical esophagostomy provides an easy, safe method of gavage feeding. For prolonged use it surpasses nasogastric intubation; the tube is away from the patient's face, cricoiditis is not a complication, and there is no nasal dis-

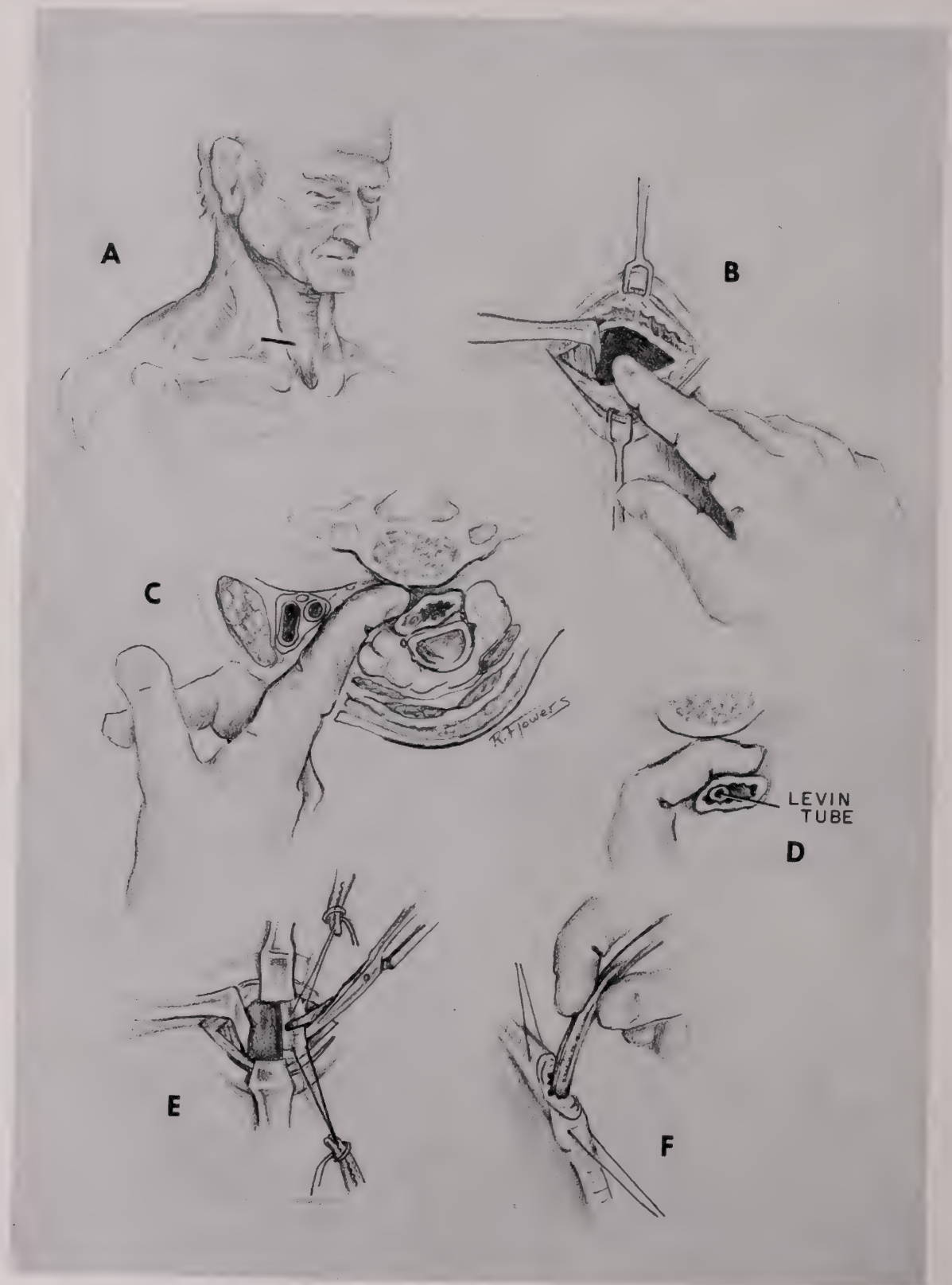


Fig. 1—Sketches showing technic of esophagostomy. A, Placement of incision; B, the sternocleidomastoid muscle retracted laterally; C, palpation of the body of lower cervical vertebra; D, mobilization of the esophagus; E, traction sutures placed in the esophagus; F, feeding tube inserted through esophagostomy.

comfort. It is a safer, simpler procedure than the gastrostomy which, in time, may leak irritating juices on the abdominal skin. Reflux is no problem in cervical esophagostomy where the advantages are simplicity of technic, effectiveness, and comfort of the patient.

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Shattuck W. Hartwell, Jr., M.D.†
Cleveland, Ohio

*Former Fellow, Department of Plastic Surgery, Cleveland Clinic, Cleveland, Ohio. Presently at the Straub Clinic, Honolulu, Hawaii.
†Department of Plastic Surgery, The Cleveland Clinic Foundation, Cleveland, Ohio.

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2. Ketcham, A. S., and Smith, R. R.: Elective Esophagostomy. Amer J Surg 104:682, 1962.
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Doctor-Patient Relationship

Historians sentimentalize the practical values of ancient medicine. One scans the pages of Hippocrates in vain for any treatments of specific value. The pages of medical history read like the log of an old-fashioned ocean voyage, in which it is noted that on such a day a whale spouted, on such a day a flying fish was sighted, or a bit of driftwood, but in which no mention is made of the huge prevailing fact that what was constantly seen day by day, almost to the exclusion of other sights, was the unending green waste of water. And this inevitably circumambient ocean is, by analogy, in medical history the "personal relationship between doctor and patient."*

*W. R. Houston in Richard M. Magraw: Ferment in Medicine, 1966.

The Progress Notes of Hippocrates

In Larissa,* a young unmarried woman was seized with a fever of the acute and ardent type; insomnolency, thirst; tongue sooty and dry; urine of a good color, but thin. On the second, in an uneasy state, did not sleep. On the third, alvine discharges copious, watery, and greenish, and on the following days passed such with relief. On the fourth, passed a small quantity of thin urine, having substances floating towards its surface, which did not subside; was delirous towards night. On the sixth, a great hemorrhage from the nose; a chill, with a copious and hot sweat all over; aprexia, had a crisis. In the fever, and when it had passed the crisis, the menses took place for the first time, for she was a young woman. Throughout she was oppressed with nausea, and rigors; redness of the face; pain of the eyes; heaviness of the head; she had no relapse, but the fever came to a crisis. The pains were on the even days.†

Editor's Note: Ovulation pain and vicarious menstruation.

*Larissa—a Greek city in Eastern Thessaly.
†Hippocrates.



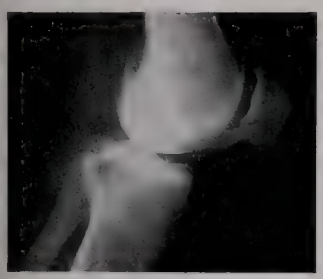
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Precautions: Before prescribing, carefully select patients, avoiding those responsive to routine measures as well as contraindicated patients. Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patient should not exceed recommended dosage, should be closely supervised and should be warned to discontinue the drug and report immediately if fever, sore throat, or mouth lesions (symptoms of blood dyscrasia), sudden weight gain (water retention), skin reactions, black or tarry stools or other evidence of intestinal hemorrhage occur. Make complete blood counts at weekly intervals during early therapy and at 2-week intervals thereafter. Discontinue the drug immediately and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.
Adverse Reactions: The more common are nausea and edema. Swelling of the ankles or face may be minimized by withholding dietary salt, reduction in dosage or use of diuretics. In elderly patients and in those with hypertension, the drug should be discontinued with the appearance of edema. The drug has been associated with peptic ulcer and may reacti-

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vate a latent peptic ulcer. The patient should be instructed to take doses immediately after meals or with milk to minimize gastric upset. Drug rash occasionally occurs. If it does, promptly discontinue the drug. Agranulocytosis, exfoliative dermatitis, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis) or a generalized allergic reaction similar to a serum sickness syndrome may occur and require permanent withdrawal of medication. Agranulocytosis can occur suddenly in spite of regular, repeated normal white counts. Stomatitis, salivary gland enlargement, vomiting, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported. While not definitely attributable to the drug, a causal relationship cannot be excluded. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, hypersensitivity, angiitis, pericarditis and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.

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Abstracts, Briefs and Commentaries

GAUCHER'S DISEASE

Twenty cases of Gaucher's disease are reported with particular emphasis on the skeletal manifestations of the disease. A summary of all of the cases is presented as well as many illustrative roentgenograms.

The femur was usually the first, as well as the most frequent, bone to be affected by Gaucher's disease. All patients showed roentgenographic changes in the femoral head or diaphysis. Pathologic fractures of the proximal femur occurred in eight femora in seven patients. Healing was delayed. Avascular necrosis of the femoral head was the most common symptomatic skeletal lesion and occurred in 15 patients, bilaterally in six children and in three adults. The necrosis healed in one seven-year-old child, but recurred at the age of 19 years. Three patients had necrosis of the humeral head—two bilaterally. Other bones affected with the Gaucher's process were radius, ulna, tibia, talus, skull, and vertebral bodies. The thrombocytopenia improved after splenectomy; however, splenectomy did not appear to influence the onset or progression of skeletal manifestations of Gaucher's disease. Roentgentherapy was of little value and may have had adverse affects in the treatment of this disease. The effectiveness of nonweight bearing for treatment of necrosis of the femoral head in children could not be determined, but may result in a more congruous head. In adults, early replacement with a long-stem prosthesis was the preferred treatment for necrosis of the femoral head. Other reconstructive surgical procedures were of benefit. The authors caution that meticulous attention to the prevention of infection and hemorrhage is essential.

Comment. This is a scholarly and detailed study of the orthopedic problems related to Gaucher's disease, and is a notable contribution to the scant knowledge heretofore available about this unusual disease.

Chester F. Fee, M.D.*
Cleveland, Ohio

Amstutz, H. C., and Carey E. J.: Skeletal Manifestations and Treatment of Gaucher's Disease; Review of Twenty Cases. J Bone Joint Surg 48-A:670, 1966.

*Fellow, Department of Orthopedic Surgery, The Cleveland Clinic Foundation, Cleveland, Ohio.

VITAMIN D

For more than 40 years it has been known that vitamin D is needed for proper growth and prevention of rickets in humans. Vitamin D has been made easily available as inexpensive vitamin supplements, in the enrichment of milk and other foodstuffs, and consequently rickets is now a rare disorder.

It is also known that vitamin D is dangerous in extremely high doses. It was originally thought that the margin of safety between the daily requirement and the toxic dosage was wide, but this range has been challenged. In 1952, reports from Great Britain and from Switzerland implied that vitamin D is the etiologic agent of unexplained hypercalcemia, and since then doses in excess of 400 units per day have been questioned.

In 1963 the American Academy of Pediatrics Committee on Nutrition published a report on the present thought in regard to vitamin D requirements and the possibility that excessive vitamin D causes idiopathic hypercalcemia. Since then it has become apparent that the severe form of hypercalcemia has its inception in utero. The later normocalcemic phase of the severe infantile form has been recognized in older children and is a severely debilitating condition. In 1965 the Committee on Nutrition recommended and amplified the following procedures: (1) continuance of the enrichment of all types of milk with vitamin D at the level of 400 I.U. per quart; (2) discontinuance of vitamin D supplements in all other foodstuffs; (3) adjustment of all vitamin D supplements to contain 400 I.U. per recommended daily dose; (4) assessment by the physician of the patient's dietary intake of vitamin D before he prescribes specific vitamin D supplements.

K. H. Heasley, M.D.*
Cleveland, Ohio

American Academy of Pediatrics Committee on Nutrition: The Relation Between Infantile Hypercalcemia and Vitamin D—Public Health Implications in North America. Pediat 40:1050, 1967.

*Fellow Department of Pediatrics, The Cleveland Clinic Foundation, Cleveland, Ohio.

Your Health—Mr. President

In a review of the actual causes of death among the first 30 Presidents, seven died of cerebral hemorrhage—John Quincy Adams, John Tyler, Millard Fillmore, Andrew Johnson, Chester Arthur, Warren Harding, and Franklin Roosevelt.

The next largest group consists of the five Presidents who died of coronary disease—James Madison, Rutherford Hayes, Grover Cleveand, Theodore Roosevelt, and Calvin Coolidge.

Four Presidents died of congestive heart failure—John Adams, James Monroe, Martin Van Buren, and William Howard Taft.

Pneumonia caused the death of three Presidents—William Henry Harrison, James Buchanan, and Benjamin Harrison.

Chronic intestinal infection claimed the lives of three Presidents—Thomas Jefferson, James Polk, and Zachary Taylor.

Of the remaining Presidents, Franklin Pierce died of cirrhosis of the liver. The majority of the evidence points to pulmonary tuberculosis as the cause of Andrew Jackson's death. Ulysses Grant died of cancer of the tongue, tonsil, and larynx, and Woodrow Wilson of cerebral thrombosis. George Washington died of acute streptococcic pharyngitis.

The final three Presidents, Abraham Lincoln, James Garfield, and William McKinley, died by assassination, in each case from gunshot wounds.*

*Karl C. Wold, M.D.: Mr. President—How Is Your Health?

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1. Stern, S.B.: Med. Times, Oct. 1967
2. Reports on 1200 patients, data in files, Warren-Teed Pharmaceuticals, Inc. 1966

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Contraindications: Because of the danger of hypermagnesemia, MAGAN is contraindicated in cases involving advanced chronic renal insufficiency. MAGAN, as other salicylates, may counteract the effect of uricosuric agents, and should not be prescribed for patients on such drugs.

Warning: As with all salicylates, high dosages of MAGAN should be avoided entirely or administered with caution to patients with liver damage, preexisting hypoprothrombinemia, vitamin K deficiency, and before surgery.

Adverse Reactions and Precautions: The same precautions applicable to salicylate therapy in general should be followed in prescribing MAGAN. Appropriate precautions should be taken in prescribing MAGAN for persons known to be sensitive to salicylates. If reaction develops, drug should be discontinued. Dosages of anticoagulants should be reduced with the administration of high dosage levels of MAGAN. *Impaired Renal Function:* Appropriate precautions should be taken in administering MAGAN to patients with any impairment of renal function including discontinuing other drugs containing magnesium and monitoring serum magnesium levels particularly if dosage levels of MAGAN are high. *Salicylate Poisoning:* Symptoms of salicylism, resulting from high doses of MAGAN, can be expected to resemble closely in character and intensity those associated with aspirin poisoning. These range from dizziness, drowsiness and ringing in the ears to vertigo, convulsions, coma and hypokalemia. Salicylate poisoning can be treated by intravenous fluids with sodium bicarbonate or lactate and potassium supplementation. In very severe cases, hemodialysis may be necessary. Vitamin K, 5-20 mg. orally or slowly i.v., usually restores the prothrombin time to normal.

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Special Article

Treatment of Cancer of the Breast

Biological Considerations*

GEORGE CRILE, Jr., M.D.†
Cleveland, Ohio

THE TREATMENT of cancer of the breast is a subject that stands on the frontier of medical knowledge where little of the truth is as yet known. Although we know little about cancer, several facts are apparent. One of the most disheartening of these is our world-wide failure to control the age-adjusted death rate from cancer per hundred thousand persons. Perhaps we have gained in regard to a few specific types of cancer, but in regard to most of the major cancers—cancer of the breast is as good an example as any—the death rate remains constant. This, despite efforts of surgeons to perform wider excisions and more radical procedures, and despite better than ever radiation therapy. The fact of there being no change in the death rate, highlights a paradox: in regard to almost any type of cancer studied, there has been progressive improvement in the cure rate. What is the explanation?

It is impossible to reconcile a rising cure rate with a constant death rate unless a third factor is introduced. This is the recognition rate, and in cancer it is rising rapidly. More frequent diagnosis of cancer leads to the inclusion of many cancers of borderline malignancy, such as papillary carcinomas of the thyroid, rectal polypoid carcinomas, intraductal cancers of the breast, prostatic microcarcinomas, and in-situ cancer of the uterine cervix. These and many other types of low-grade cancer treated successfully increase the five-year cure rate. Earlier treatment of cancers that ultimately prove fatal also increases the five-year cure rate by enabling a higher proportion of patients to survive for five years, even though the patients die within a year or so later. But neither of these factors influences the death rate per 100,000 persons. As McKinnon[1] has said: "We do not alter the death rate from cancer by curing cancers that would not have been fatal even if untreated." Unless the now-fatal cancers are

*Taken from "A Biological Consideration of Treatment of Breast Cancer," by George Crile, Jr., published by Charles C. Thomas, Publisher, Springfield, Illinois, 1967, by permission of the publisher.

†Department of General Surgery, The Cleveland Clinic Foundation, Cleveland, Ohio.

treated with improved methods, the death rate per 100,000 persons will remain unchanged. That is our problem.

McWhirter[2] has shown that if a cancer starts as a single cell it can be estimated that it would take 20 divisions of that cell and all its descendants to make a mass 1 mm in diameter. Thirty cell divisions would be required to make a mass 1 cm in diameter: forty divisions and the tumor would weigh more than one pound; fifty divisions and it would weigh more than 1000 pounds. The growth of cancer follows an exponential curve that at first rises slowly and then heads skyward as the doubling goes on. A tumor that grows exceedingly fast may double its size once a month. A slowly growing tumor, like a scirrhous cancer of the breast, may not double its size in a year. If we correlate these rates of doubling with the number of cell divisions that are required to make a mass 1 cm in diameter, it is clear that a rapidly growing tumor, that doubles its size once a month, must have been present for at least 30 months before it reached the size of 1 cm. A slowly growing tumor that doubles at the rate of once a year must have been present for 30 years or longer to have attained that size. The tiny scirrhous cancer discovered in the breast of a 70-year-old woman may have started growing when she was 30 or 40 years old. But from the time the tumor 1 cm in diameter is discovered, it might take less than 10 years for it to grow to weigh more than a pound. In view of the long history of such a cancer, and the probability that during much of its life history it was capable of metastasizing, it is small wonder that earlier treatment has done little to control the ultimate death rate from such cancers.

Until we know more about the factors that control the spread of cancer, we should not generalize about the subject of cancer. At present there is no scientific basis upon which anyone is justified in advocating simple mastectomy, radical mastectomy, ultraradical mastectomy, or irradiation therapy as the single or even the chief method of treatment of cancer of the breast. There may be a place for all of these types of treatment, for, just as there are three types of cancer of the skin—basal cell, squamous cell, and melanoma, so there may be at least three biologic types of cancer of the breast. If so, each may respond best to its own type of treatment. The challenge to the surgeon is to try to find a way to distinguish each of these biologic types from the others. Individualization deserves more emphasis than it has been given in our cancer clinics in recent years.

Although our understanding of the factors that cause cancer has increased a great deal, the clinical approach to the problems of treatment has changed little. In most cases, adequate operations performed as early as possible still seem to afford the best chances of cure. Radiation applied to localized and radiosensitive lesions is often equally successful.

Genuine advances have been made in endocrine control of endocrine-dependent tumors. Chemotherapy is used for a few types of cancer, usually for palliation only. Although immunologic methods of controlling cancer have not as yet been successful, possibly in the future this line of attack will be more effective than any of the new, established methods. Moreover, there may be merit in attempting to preserve and enhance what natural immunity the host may have against this tumor.

The most hopeful aspect of the cancer problem is our increasing knowledge of the factors that control differentiation, mutation, and growth. We now recognize the cell's ability to adapt its enzyme system to environmental changes; we recognize that there are factors in embryonic life which regulate cell differentiation; we are beginning to study the interplay of the local and the systemic factors that control cellular growth. These advances and an increasing understanding of the genetic mechanism of the normal cell make it likely that soon we shall have better understanding and more effective treatments of cancer.

One of the most promising areas for research is study of the local factors that control normal cellular growth. If the chemical substances that control the growth of each type of cell could be identified and made available, it is likely that they could be used to prevent the development of many cancers, and to control the growth of these cancer cells that have not attained complete autonomy of growth.

Our thinking about cancer has come a long way. At least we can view it not as a demon to be exorcised, but rather, in its true biologic

perspective as an unwanted phenomenon of growth. Progress comes through understanding the ways of nature rather than from trying to bend them to our will. Only after we understand the factors that control the growth of normal cells will the problems of cancer be solved.

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2. McWhirter, R.: Some Factors Influencing Prognosis in Breast Cancer. J Fac Radiol 8:220, 1957.

Epilepsy and the Moon

The medical theories prevailing in eighteenth century United States and their formidable therapeutic application are well illustrated by the treatment of an epileptic Negro slave by a Virginia physician, in a manner which ample evidence indicates was not unusual:

"When first he came to me I put him on a course of Cumabarine Medicines. I bled him, in the fit, vomited him afterwards and . . . gave him aorthrementics and mercurial purges. All this seemed to do no good. I therefore Resolved to give him a shock from the two Glass Spheres fixed to an Electric Machine, but before I could get it completely fixed I drew a blister on the scalp behind—upon the Occupit, dressed it according to Art and made it perpetual, at the same time putting him under a different course of Medicines than had been tried before. The Blister ran Bountifully for a while; but drying, I laid another upon the nape with an Intent to Stimulate a Branch of a Considerable Nerve Called par Vagum which in that part Lays Something Superficial, continuing the Medicines with little Alteration. This succeeded and the next Change of the Moon expecting the fit, as usual, he missed them. The Medicine has been continued and he has missed the fits this last full moon again. The Blister is almost dry but I intend if the fellow stays with me to draw a fresh one. It is something remarkable that the fits has Usually returned when the Moon was in the Sign Capricorn Even When it was a week before or after the full or change."*

*Bernhard Stern: Society and Medical Progress, 1941.

Incubation

I began practicing medicine at the age of eight, on the cat. I mixed weeds with chopped-up angleworms and, adding a little water, put the infernal mess in green glass bottles, letting it stand in the hot sun of the Middle West for several days until the mixture was ripe.

I suppose nothing ever had a more unholy smell; that was my only standard of medical potency. I fed little spoonsful of it to my gray cat, who yowled and fought like a child taking castor oil. Then I spent hours holding it and loving it, keeping away from the house and the family till its paroxysms were abated.

Every day of my life I looked forward to being a doctor. I never knew why, and I don't remember that the reasons even interested me.*

*Frederic M. Loomis (1877-1949) in Why We Became Doctors edited by Noah D. Fabricant, M.D., 1954. Editor's Note: Frederic Loomis became a gynecologist and obstetrician.

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History of Medicine

The Cleveland Clinic Foundation

FAY A. LeFEVRE, M.D.*
Cleveland, Ohio

THE CLEVELAND CLINIC opened its doors to patients and began the practice of medicine in February of 1921, incorporated in the State of Ohio as a nonprofit institution. It was founded by four physicians whose medical achievements became known throughout the world—George Crile, M.D.; Frank Emory Bunts, M.D.; William Edgar Lower, M.D.; and John Phillips, M.D. (Figure 1). Doctor Crile, Doctor Bunts, and Doctor Lower had practiced together many years as a "team" before the official opening of the Cleveland Clinic, the original building of which is shown in Figure 2. They believed that the team approach to the practice of medicine would best serve the patient, and that the group practice of medicine would most fully achieve three special goals they set for the Clinic: *Better care of the sick, further study of their problems, more teaching of those who serve* (Figure 3).

A brief mention of the organization and the facilities of the Cleveland Clinic follows.

The Cleveland Clinic Foundation is governed by a Board of Trustees comprised of a group of prominent businessmen and members of the professional staff. A Board of Governors, consisting only of members of the medical staff, is responsible for all medical phases of the Clinic and the Hospital.

The Cleveland Clinic Foundation is comprised of three units: the Cleveland Clinic, the Cleveland Clinic Hospital, and the Division of Research. The Cleveland Clinic Educational Foundation is a separate corporation affiliated with The Cleveland Clinic Foundation. The Cleveland Clinic has four primary medical divisions—Medicine, Surgery, Pathology, Radiology—and each of these divisions is organized into specialty departments. The professional staff number 150 physicians and doctors of philosophy, and 270 fellows and interns who participate in thirty-one educational programs with a view to qualifying as certified specialists. A total of 2500 employees serve as supporting personnel. The physical facilities, composed of buildings, parking lots, and equipment, cover approximately three city blocks on the east side of the city of Cleveland.

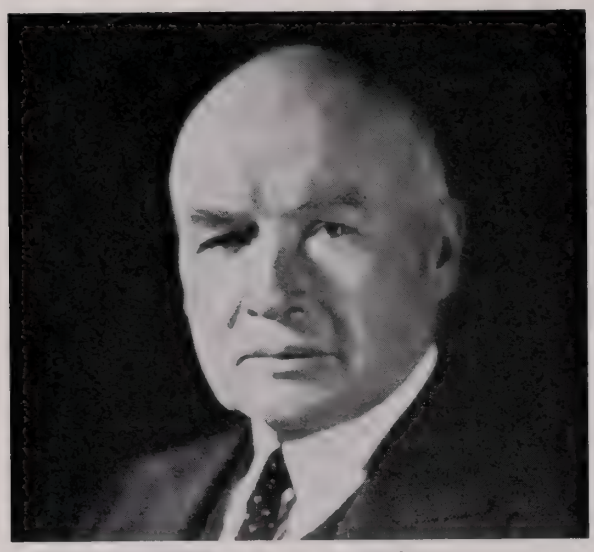
*Chairman, Board of Governors, The Cleveland Clinic Foundation.



George Crile, M.D.



Frank E. Bunts, M.D.



William E. Lower, M.D.



John Phillips, M.D.

Fig. 1—The four founders of the Cleveland Clinic



Fig. 2—Original building constituting the Cleveland Clinic in 1921.

The 10-floor Main Clinic Building has in it physicians' offices, examination rooms, laboratories, waiting rooms, business offices, the telephone operators, the Department of Photography, and the Department of Medical Illustration.

The Central Building, with a curved-drive entrance (Figure 4), joins the Main Clinic Building and the Hospital and provides additional space for clinic practice, for research projects, for laboratories, and for business operations; and it has a first-floor automated snack bar. The Cleveland Clinic Pharmacy is across the street from the main entrance and adjoins the largest Clinic parking lot.

The Cleveland Clinic Hospital has 650 beds, 26 operating rooms, and a cafeteria; a tiny, lovely, nondenominational chapel adjoins the lobby and is accessible at all times. The hospital has two unusual features: a five-bed Kidney Dialysis Unit and a Cardiovascular Unit. The Kidney Dialysis Unit is the second one in the United States to use the new method of having the dialyzing solution mixed in a master control room and piped to each patient's bed where it is used for one complete circuit of the patient's blood, then is discarded, and is replaced from the control room. The Cardiovascular Unit is a 39-bed unit that is entirely self-contained, even having its own three operating rooms and radiologic service. It has a 15-bed intensive care section (Figure 5) with all the modern safeguards for the patient, where he remains under close, skilled scrutiny until he is ambulatory and can be transferred to a general medical-surgical nursing floor in the hospital.

For many years research has played an important part in the activities of the Foundation. Time and facilities are provided to members of the professional clinic staff for approved research projects. The majority of the research, however, is conducted by the staff of the Division of Research, which occupies a separate building adjoining the Hospital and the Clinic. The total research group, including full-time members of the staff, Research fellows, and supporting personnel, comprises more than 60 persons. Programmed research is related chiefly to cardiovascular disease, with special interest directed toward hypertension and arteriosclerosis. In addition to the cardiovascular program, research in the area of immunology as it relates



Fig. 3—Bronze plaque commemorating the four founders of the Cleveland Clinic and their goals.



Fig. 4—The Central Building of Cleveland Clinic joins the Main Clinic Building (on the right) with the Cleveland Hospital (on the left).



Fig. 5—Intensive care section of the Cardiovascular Unit in the Cleveland Clinic Hospital.



Fig. 6—The Education Building, with auditorium, offices, the Medical Library, and three floors of one-person bedroom studies for fellows and interns.

to organ transplantation is being developed. Every effort is made to relate program research to clinical medicine, resulting in close cooperation between the research and clinical staffs. Financial support for the research programs comes from the Foundation and its endowments, from private foundations, and from the National Heart Institute.

The seven-story Education Building (Figure 6) was completed in 1964: the gift of a grateful patient. In the Education Building is the Bunts Auditorium that seats 272 persons. There, throughout the year, are held fifteen two-day postgraduate seminars on various medical subjects of timely interest. Physicians from all over this country and from Canada attend the meetings. Outstanding guest lecturers are featured on the program along with our own staff physicians.

In the Education Building are the offices of the Director of Education, the Reprint Room, the staff physicians' lounge, offices for emeritus staff members, and six completely equipped seminar rooms. Also in this building are the 15,000-volume Medical Library and the Editorial Department where the *Cleveland Clinic Quarterly* (publication of medical papers written by staff physicians and fellows) is prepared for the printer. The top three floors of the Education Building have 63 one-person bedroom studies for residents and interns; on each floor is a recreational lounge. A closed ramp leads from the fifth floor directly to the sixth floor of the hospital for the convenience of fellows on call.

A guest motel is now under construction across the street from the hospital and will include an indoor swimming pool and a sauna room. A second-floor ramp will connect the two buildings. The motel will have direct access to the facilities of the 150-room Bolton Square Hotel, where patients and their families and many Clinic nurses are housed.

The many modern structures that have met the needs of a growing medical service now surround the North Clinic Building, the Clinic's first building in 1921. A great many changes have taken place in the forty-seven years since the Cleveland Clinic was organized, not only in the development of the physical facilities, but in the training of residents and interns, and in diagnostic and therapeutic technics. In the pre-

ceding pages of this issue of *Minnesota Medicine,* Cleveland Clinic staff members present scientific reports of their clinical experiences, an editorial, and a clinicopathologic conference; and a special section comprises reports by some of our resident physicians.

Speakers' Bureau

It is generally agreed that, ideally, anesthesia should be administered by or under the direct supervision of a physician with training and experience in anesthesiology. But anesthesiology, like many other medical specialties, has such a serious manpower problem that it is not likely that this desirable goal can be achieved in the foreseeable future. Locally, anesthesiologists are in such short supply that their services are directly available in only a small fraction of Minnesota communities. The ultimate responsibilitiy for anesthetic administration therefore often falls wholly upon the patient's family physician who must then delegate it to an assistant—often an individual without medical, training and with limited technical background and experience.

In an effort to furnish interested practitioners with help in this dilemma, the Minnesota Society of Anesthesiologists has established a Speakers' Bureau whose purpose is to provide physician and paramedical groups with authoritative information about anesthesiology and related subjects. A roster of experienced speakers is available for assignment to regional and local programs upon request by a sponsoring group.

The speakers strive primarily to provide solutions to common clinical problems by emphasizing basic principles and citing new knowledge. Their subject matter deals directly with anesthesia and its complications, and with allied topics such as resuscitation, therapy of chronic pain, management of respiratory failure, hypotension and the like.

The Society invites medical staff and county medical society officers involved in program planning to avail themselves of the services of this new Speakers' Bureau. Requests should be directed to either of the Bureau's co-chairmen, Joseph J. Buckley, M.D., Department of Anesthesiology, University of Minnesota Medical School, or J. T. Martin, M.D., Section of Anesthesiology, Mayo Clinic, Rochester.

Minnesota Medicine Cover Photographs

In order to encourage more physicians to submit color slides for use on the cover of MINNESOTA MEDICINE the competition is being discontinued. The picture editor now invites all physician-photographers to send 35 mm. color slides of suitable subjects for consideration as cover pictures. The format must be horizontal because of printing limitations. Pictures high-lighting Minnesota seasons, places, and activities will have an automatic advantage. No limit as to the number of slides sent will be set, but all slides should be individually identified. All slides will be returned. Physicians whose pictures are used as covers will be recognized in MINNESOTA MEDICINE. We can use many more pictures than we have received in the past.

Classified Advertisements

Classified advertising rates are twenty (20) cents a word; minimum monthly charge $5.00; key number, fifty (50) cents additional.

Replies to advertisements with key numbers should be mailed in care of Minnesota Medicine, 375 Jackson, St. Paul, Minn. 55101.

WANTED: General surgeon, G.P. with G.P. residency or internist to join two very busy general practitioners in new, fully equipped office in Chaska, Minnesota, 25 miles from downtown Minneapolis. Accredited hospital. Salary open. Prefer military service completed. Call collect—612-448-2050 Chaska, Minnesota, Drs. Heinzerling and Pistulka.

THREE MAN group in North West Wisconsin Resort, State Conservation and Retirement Area needs two more physicians adequately to serve their practice. Facilities offered are three-room physician suites, X-ray and lab under AMT technician, RN-only nursing personnel. New accredited thirty-two bed hospital and forty-six bed nursing home. Deer and duck hunting, fishing within five minutes of town. Internist most needed; generalists welcomed. Will meet any reasonable salary request. Partnership after one year. Write: MINNESOTA MEDICINE—365; 375 Jackson St., St. Paul 55101.

WANTED: Physician wanted to join three-man group in fast-growing area just thirty minutes south of the Twin Cities. Will practice in a new clinic, new hospital and new nursing home. Salary and terms open. Contact M. H. Hunter, M.D., River's Edge Medical Clinic, Farmington, Minnesota. Telephone (612) 463-7181.

GENERAL PRACTITIONER wanted to join well-established practitioner. New clinic building—90 miles east of St. Paul—city of 14,000. Early partnership with full hospital facilities. Ideal location. L. W. Picotte, M.D.; Chippewa Falls, Wisconsin.

WANTED: YOUNG PHYSICIAN for association leading to partnership with four well-established General Practitioners in fast-growing suburb of St. Paul. Excellent clinic facilities in nearly new, partnership owned, well equipped, medical center building. Contact: A. Eugene Muller, M.D., North St. Paul Medical Center, 2579 East 7th Avenue, North St. Paul, Minnesota 55109.

GENERAL SURGEON, Certified, part or full-time association in multi-specialty clinic. Alfred F. Anderegg, M.D., 645-5851, 2500 Como Ave., St. Paul, Minnesota.

WANTED: GP to join clinic serving population area of 12,000. City has new hospital, new clinic building, two nursing homes, new Jr-Sr high school, new swimming pool, rich farming area in Red River Valley. Fishing and hunting nearby; metropolitan city close by. Salary open and partnership if interested. Write or call Warren Clinic, Warren, Minnesota 742-6231, area code 218.

DIRECTOR OF MEDICAL EDUCATION, full time —Methodist Hospital, St. Louis Park, Minnesota 55426. Contact Mr. Earl Dresser, Administrator or Dr. W. John Dawson, acting director of medical education.

WANTED: G.P. or Internist willing to do some G.P. Twin-towns totalling 12,000 western Minnesota Group now two G.P.'s and one FRCS surgeon. Modern clinic building with eight assistants, X-ray and minor laboratory, 125 bed accredited hospital. Rotating calls one night a week and every fifth week-end. Hunting, fishing, golfing available. Initial salary $1500.00 per month. Oportunity for partnership in one year. Apply to Louis T. O'Brien, M.D., Breckenridge, Minnesota.

SKIING, HUNTING, FISHING and practice of Internal Medicine offered to board qualified or certified internist by 21 man specialty clinic in northern Minnesota. Presently adding new modern facilities to keep up with rapidly expanding economy. Salary first year, shareholder status second year. Reply Russell Anderson, M.D., East Range Clinics, Ltd., Virginia 55792 or call collect, Area Code 218, 741-6244.

SEVENTEEN-MAN Wisconsin group located in college community of 40,000 with excellent hospital facilities is seeking additional associates in the following areas: (1) Internal Medicine, (2) Urology, (3) General Surgery and (4) General Practice. For further information please contact D. R. Griffith, M.D., Midelfart Clinic, Eau Claire, Wisconsin 54701.

GENERAL SURGEON interested in some general practice to associate with a 2-man partnership in a rich agricultural community in southern Minnesota. Modern hospital and new clinic building. Hunting, 9-hole golf course, swimming pool. Salary open and full partnership as soon as desired. Write: Minnesota Medicine—405, 375 Jackson, St. Paul 55101.

WANTED: General practitioner, to join two G.P.'s well established in north central Minnesota community, 2200 pop., 65 miles from Twin Cities. Excellent office space with lab and X-ray, just opened new hospital, all facilities. Assistantship or partnership. Considerable surgery and obstetrics. Hunting, fishing, golf club. Great opening for interested G.P. WRITE MINNESOTA MEDICINE—381; 375 Jackson, St. Paul, 55101.

INTERNIST AND GENERAL PRACTITIONER wanted to join a five-man clinic group in Minneapolis. Complete laboratory and X-ray with board roentgenologist. Excellent hospital staff associations. Salary arrangement to start with early partnership. Write: MINNESOTA MEDICINE—289; 375 Jackson, St. Paul, 55101.

PRACTICE FOR SALE: Well established general practice in South Minneapolis serving an excellent community, within easy reach of the finest hospitals in the State. Very reasonable, low overhead. Splendid opportunity for solo or partnership practice. Write: MINNESOTA MEDICINE-397, 375 Jackson St., St. Paul 55101.

Continued to page 1156

Law and Medicine

The Surgical Team

Legal Liability of the Individual Members

THE SURGICAL TEAM concept has become basic to the operative treatment of patients. The team is the outgrowth of the complexities of modern science, which are overwhelming and defy the understanding and the mental capacity of any one person.

The burgeoning masses of medical knowledge have taxed the ability of nearly everyone to cope with the problems presented by these changes. Scientific information accumulates more rapidly than it can be classified or applied, and the rapid technologic advances often make new pieces of equipment and technics obsolete before they can be properly evaluated. The medical profession has met the problem first by creating specialties of medicine. Thus, a young physician, a graduate of a general course in medicine, has the opportunity during residency training to concentrate his studies on a specific aspect of medicine and thereby acquire a higher degree of expertise. It becomes obvious, though, that the specialist physician, highly trained and skilled, is subject to self-imposed specialty restrictions that limit his sphere of practice. He is dependent upon other specialist physicians. But it is becoming ever more obvious that in the large medical centers of today one finds not only the major divisions (specialties) of medicine and surgery, but also many subdivisions and subspecialties in which members of the staff limit their professional activities to highly restricted aspects, as for example coronary angiography. The major specialties of yesterday have become so diversified within their own complexes that division into subspecialties has necessarily followed.

With the advent of highly sophisticated surgical procedures, it soon was recognized that during the surgical procedure the patient is well cared for by numerous persons whose vigilance and care encompass his basic physiologic requirements. Now, with the complex surgical procedures of today, the aftercare of the patient is perhaps as vitally important as the operation itself. With his expert knowledge of cardiopulmonary physiology and his skill in ventilatory technics, the anesthesiologist has had to extend his services to the postoperative period, in an effort to give the patient the most complete care possible. In the last several decades, most hospitals have created special sections where immediately postoperative care is available: the Postoperative Recovery Room, the Surgical Intensive Care Unit, the Constant Care Unit.

Serving in those units are highly trained nurses who specialize in the critical care of the immediately postoperative patients and other acutely ill patients. The concentration of the seriously or critically ill patients in specific sections within the hospital makes it possible to render the best quality of treatment with the greatest economy of professional personnel—particularly registered nurses. These special units may lower the costs of management, but the cost per patient per day in the units is increased.

Thus has medical progress brought many benefits to the surgeon and to the patient. This progress has also brought many complexities. Each specialist, in a team spirit, offers to the patient the advantage of particular skills. Each physician attending the patient participates individually, but also in the spirit of team effort. Though each physician possesses certain ethical and legal prerogatives, each must act in concert with the other consultants, thus implementing the concept of the *surgical team*.

Credit to be given:
Abstracted from the first chapter of the book: ***Law and the Physician***, (in Press) with the express consent of the copyrightholder, Williams & Wilkins Co., Baltimore, Maryland.

Nurses

The nurse's role is undergoing scrutiny by administrative officials concerned with the legal liability incurred by the nurse in the modern practice of nursing. In many respects the nurse's role is changing. Formerly the nurse was not expected to exercise judgment in the treatment of the patient, but was to carry out orders of the physician; she was not expected to originate and prescribe treatments or to make diagnoses. Such activities required the exercise of judgment. However, in the modern concept of the surgical team, the nurse is being given an increasingly responsible role in the care and treatment of the patient. An increasing number of men are becoming qualified as nurses, and male nurses supplement the staffs of many hospitals. Today physicians demand that nurses be highly trained technically and demand that they perform functions that were formerly considered far outside the nurse's prerogative. As an illustration, in the modern intensive care unit it is common for a nurse, trained in acute medicine, to institute electroshock therapy for cardioversion on a patient whose electrocardiograph monitor demonstrates ventricular fibrillation. A decade ago it would have been folly to suppose that a nurse would be defibrillating a patient's heart. Today many physicians are inexperienced in the technic, and they rely on the trained nurse to administer the new procedure of cardioversion by electroshock. It is safely practiced only under ideal situations such as exist in the intensive care units. Since the benefits of electroshock therapy depend upon early diagnosis and institution of treatment, the nurse is frequently the only trained person immediately available. When she recognizes ventricular fibrillation, she and her associates immediately institute resuscitative measures. Upon the nurse rests the life of the patient. Time is not available to await the arrival of a house physician. Thus with the acute shortage of physicians, more and more medical duties are being delegated to those who are not physicians. Many duties involve diagnosis and treatment; admittedly some even include the exercise of medical judgment. While this is thought to be legally, and by some ethically, incorrect, nonetheless it is an established practice in many modern institutions. Far from being restricted, such activities and others by nurses are being established as part of the duties of a nurse trained in acute medicine. This expansion of performance does most emphatically not entitle nurses to practice medicine, however. The above practices have been accepted generally by the profession and therefore, at least in my opinion, will be adopted by the law. The nurse is still following instructions established by the staff. Being an employee of the hospital, and carrying out routine duties not in the presence of the attending physician, the nurse is formally responsible for her acts of negligence, and the hospital is vicariously liable as her employer.

The Referring Physician

In many medical circles there is much discussion relative to the necessity of referring patients to medical centers and to the care of specialists. It is a legal axiom that consultation with another physician, particularly a specialist, is one of the great advantages if a malpractice action should result from the physician's treatment of the patient. In legal circles there has been increasing discussion relative to the degree of skill and care that must be exercised by the physician in various localities. There is no doubt that the physicians' standards differ, that is, the degree of skill of the expert must certainly, in most instances, differ from that of the general practitioner. The specialist represents himself to the public as being expert in a specific field. Therefore, according to the law, he is expected to exercise a higher degree of skill than those not expert in that field.

A physician is held to that standard of practice which is adhered to by other physicians in the same or similar community. Evidently the rule was promulgated upon the basis that all communities do not have equal facilities or physicians of equal training. For instance, a rural practitioner is certainly not expected to be as highly trained as the specialist in the large medical center. It would be grossly unfair to require the general practitioner in a rural community to have the latest diagnostic equipment, to have the facilities of the large medical centers, to have the opportunities for learning the latest developments in the field of medicine, or to have the experience of a phy-

sician who specializes within an exceedingly narrow field. Therefore the standards of practice do vary. However, the standard of practice of specialists probably does not vary as to the degree of skill. It is conceded that the degree of care required of a specialist is the same as that which is demanded of a general practitioner. "Care," in the law, is equated with and defined by the word "diligence." The law requires all physicians to be equally diligent in the care of their patients. It is the degree of skill that varies. Between specialists the degree of skill does not vary from community to community according to many of the recent decisions of the courts. Though the degree of skill of a general practitioner in a rural community is not expected to be equated with that of the medical center specialist, both types of physician must exercise the same degree of diligence.

In summary, all physicians—whether specialists or generalists—are expected to exercise the same degree of diligence in the care of their patients. The degree of skill exercised, though, depends entirely upon whether or not the physician considers himself a specialist. In either case, whether he is a generalist or a specialist, the physician is expected to exercise reasonable skill according to his role.

In the case of the generalist, the local standards are usually invoked. That is, the general practitioner is expected to exercise that degree of skill and care equivalent to that which is exercised by physicians operating under like circumstances and in the same or similar community.

On the other hand, when a physician considers himself a specialist, it is generally conceded that he is a diplomate of the American Board of his specialty. To be thus certified, the physician must have met all of the strict national requirements. In many recent decisions, the courts have taken cognizance of the fact that a physician is an expert by virtue of the fact that he is a diplomate of the American Board of his specialty. It is routine for counsel, when placing a physician upon the stand, to qualify him before the court and jury by asking direct questions as to his training and certification. Invariably, a surgeon, for instance, is asked if he is a member not only of his local, state, and national medical societies, but also if he has been certified by the American Board of Surgery, and whether or not he is a Fellow of the American College of Surgeons. Thus, both by procedural practice and by court decision, the standards of practice of the physician are gradually changing from those of yesteryear. The standards of community practice at least in regard to specialists are gradually being changed from those affected by local influence to those representing national trends.

Group Practice

The concept of the surgical team can be likened to the association of physicians who cooperate in a clinic type of practice or group practice. There was a time when the physician set up practice merely by hanging up his "shingle." Many times his office was in his home and his equipment consisted of a few diagnostic instruments such as a stethoscope and a blood pressure cuff, and a few pills and elixirs, but few specific agents. His accounting system was very simple. Not being versed in business practices, he did not keep financial records. Today the modern medical office requires the outlay of rather large sums of money for sophisticated medical equipment, both diagnostic and therapeutic. Equipment purchased today may well be rendered obsolete with the advances in medical science tomorrow. Modern business systems maintain records of the medical practice and render financial statements.

Surgical Consultation

Relatively few patients consult a surgeon directly. In most instances, the surgeon is merely a consultant to the internist, the generalist, or the family physician.

The system of referring patients to consultants who are specialized in individual fields of medicine is well established and cannot possibly be used as evidence against the referring physician. In fact, quite the opposite is usually held by courts. If this were not so, then any physician would be considered to offer prima facie evidence of his own incompetency when he recommended that a patient consult another specialist or be transferred to a medical cen-

ter. If such were the general rule of law and principle of ethics, then there would be no referrals to physicians more expert in the treatment of a given condition and thus the patient would be denied such care. The question often arises as to the liability of this referring physician and to that of the consultant. It is a general principle of law that when the referring physician relinquishes direction and control of the treatment of the patient to another physician, he is no longer responsible for the patient's welfare or for the performance of any negligent acts of the specialist. As one court has stated:

> "* * * A doctor cannot practice his profession by proxy, so, if he sends another physician to treat a patient or perform an operation and the substitute is accepted by the patient, the doctor is not liable for the independent acts of the substitute; but where a physician retains complete control and renounces no part of his functions as sole physician, but delegates to another the manual administration of the prescribed treatment, the relation of principal and agent exists, whether the person administering the treatment be a layman, a physician, or a nurse."

However, if the referring physician calls in a consultant and shares responsibility for the case, the question of liability becomes rather complicated.

In the surgical team concept and according to the regulations of many hospitals, the patient must be admitted to a primary service. In some institutions patients are admitted to joint services: that is, there are two primary treating physicians: the surgeon and the internist. Perhaps in these institutions both physicians would be considered to be treating physicians and thus primarily responsible for their own spheres of influence. There are few court decisions involving members of the surgical team; therefore some legal details remain unclear. While there seems to be little difference in the role of consultants vis-a-vis the role of the individual members of the surgical team, perhaps there may be some important technical differences.

Today, although the surgeon may represent the primary service, his role sometimes is rather minor in comparison to the roles of others on the surgical team. In this situation plaintiff lawyers name all the members of the surgical team: nurses, physicians, orderlies, and others, the hospital, and a pharmaceutical or equipment manufacturer, in any suit. Each defendant disclaims responsibility and thus enables the plaintiff to "make his case" on his opposition. The surgeon too dislikes individual legal liability and is most eager to share responsibility with all members of the surgical team.

Physician-Patient Relationship

It becomes evident that in the modern concept of the surgical team, each member must establish rapport with the patient. Without question the surgeon must confer with the patient or the patient's family concerning the intended surgical procedure. The fact that the surgeon has a crowded professional schedule does not release him of legal liability to communicate with the patient or those responsible for him. Lack of rapport is probably the most important single cause of malpractice action against a physician. Indeed, it was lack of physician-patient rapport that led to the development of what has been termed "informed consent."

The patient who is unaware of the full implications of the surgical procedure contemplated might well have not given an adequate legal consent for the procedure. It is axiomatic in the law that all patients who enter a hospital under the doctrine of the assumption of risk, at least impliedly grant permission or consent or authorization for treatment. However, in the modern hospital, the possibility of an unauthorized treatment being instituted assumes great importance. The present-day surgical team might consist of more than a surgeon and an anesthesiologist. Many persons may be involved. Each by his individual role—unless each clearly explains his function and activities to the patient—may commit a surgical or medical assault and battery upon the patient.

Any association of physicians may lead to legal entanglements. Irrespective of the fact whether the agreement of association is based on accounting or bookkeeping and office-sharing or equipment-sharing, there may well be in law an *agency by estoppel* established between these several members of such an agreement. The fact that no formal partnership papers have been drawn does not preclude the

possibility of the existence of such an agency between a physician and the surgical team. In formal partnerships each physician is an agent of the partnership and the actions of any one partner may well bind the others. Therefore it is incumbent upon each physician contemplating such an association with another physician to consult an attorney for his advice and guidance. Indeed, if any agreement is established it is strongly recommended that such a contract or written instrument be reviewed periodically in order to determine whether it does in fact express the intent and present objectives of those in the association.

One serious fault of some physicians is their failure to know their limitations. It is recognized that a physician in an isolated community will be faced with serious surgical emergencies that he is not trained to treat. His rendering of emergency aid to a patient does not subject the treating physician to other more stringent rules than the exercise of reasonable care and skill. However, this same physician may not with impunity undertake to perform complicated elective procedures under the supposition that he may assume the legal protective cloak he may enjoy in emergency situations. In regard to such elective operations, he may be held to the standard of care and skill of the surgeon who is expert in the field.

In a hospital where professional qualifications are not investigated thoroughly, or where the rules of the staff are not enforced strictly, some physicians will perform operative procedures in which they have little or no training. It must be understood that the law will require them to have reasonable skill. Should a surgeon wish to carry out a new procedure, or one with which he has little experience, then the patient should be apprised of this fact.

The interrelationships of the members of the surgical team become increasingly difficult to differentiate and may lead to many possible legal complexities. A physician, as a member of the team, becomes professionally dependent on others on the team, and his legal responsibility thereby becomes more and more involved with that of his associates.

Carl E. Wasmuth, M.D., J. D.*
Cleveland, Ohio

*Head, Department of Anesthesiology, The Cleveland Clinic Foundation; Adjunct Professor of Law and Director of Division of Legal Medicine, Cleveland-Marshall College of Law, Cleveland, Ohio.

Diagnostic Acumen

The physician should be of tender disposition, of wise and gentle nature, and more especially an acute observer, capable of benefiting everyone by accurate diagnosis, that is to say, by rapid deduction of the unknown from the known. And no physician can be of tender disposition if he fails to recognize the nobility of man; nor of philosophical nature unless he be acquainted with Logic; nor an acute observer unless he be strengthened by God's guidance; and he who is not an accurate observer will not arrive at a correct understanding of the cause of my ailment.*

*Edward Browne: Arabian Medicine.

The true test of civilization is, not the census, nor the size of cities, nor the crops, but the kind of man that the country turns out.—Emerson

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This also is a season of discovery. A lot of presidential timber is finding out it's nothing but kindling.—Changing Times

(Continued from page 1150)

THE WEST MEDICAL CLINIC has an opening for a General Practice Physician, on October 1, 1968. This is a five man group that conducts a practice near downtown St. Paul and also, has the Airport Medical Clinic at Wold Chamberlain Field, Twin City International Airport. Both clinics have full laboratory and x-ray services with technologists covering both fields.

The Airport Medical Clinic does industrial, occupational and Aviation medicine. FAA examinations are conducted at both clinics.

The clinic located near downtown St. Paul has a practice limited principally to internal medicine, pediatrics, as well as occupational and industrial medicine. There is only a limited practice of obstetrics and no surgery.

Salary is open and opportunity for partnership is available. Write: West Medical Clinic, 539 W. Seventh Street, St. Paul, Minnesota 55102. Phone: Area Code 612-227-9341.

FOR SALE: Practice—clinic—apartment bldg.—military-exempt town—will retire—14-room clinic-dental suite; four apartments. Apartments will retire costs. Two good schools and churches—good farming area. New large swimming pool—18 hole golf course playable this summer—theatre—bowling alley. 17 miles from St. Olaf Hospital, Austin. Write—P. J. Schneider, M.D., Adams, Minn. 55909.

FOR SALE: 1. Ritter Table—all purpose, with electric hydraulic lift and manual tilt, excellent condition, less than 50% of replacement. 2. Burdick Ultra Sound, perfect working order. 3. Office Scale. 4. Cole Metal Desk, double pedestal, matching swivel and arm chairs, sandalwood. 5. Trial Lens Set. 6. Disposable Sigmoidoscope Rechargeable. 7. Older X-Ray Unit, fixed table, 100 ma, stainless steel developing tanks. J. T. Adkins, M.D., 612-427-2079 (home) or 612-755-1621 (office).

ANOKA-MINNEAPOLIS excellent openings for psychiatrist—unit chief & staff physicians. 600-bed open-door hospital. Salary $16-$28,500. Apply Medical Director, Anoka State Hospital, Anoka, Minnesota 55303.

DOCTOR WANTED: General practitioner to join growing practice in aggressive Northwestern Minnesota community of 750. Trade area numbers in excess of 5000. Average age of 30 key businessmen in community is 36. Eighteen bed hospital operating and plans are currently in formation to add to acute bed numbers plus construction of a nursing wing. Direct inquiries to Joel Spilde, Administrator, Karlstad Memorial Hospital, Karlstad, Minnesota 56732. Telephone 218-436-3375.

WANTED: General practitioner to join two young general practitioners in well-established practice in suburban St. Paul. Excellent office space with lab, x-ray, and emergency room. Salary negotiable, with an association leading to early partnership opportunity. Write MINNESOTA MEDICINE 412, 375 Jackson St., St. Paul 55102.

PRACTICE AVAILABLE: A well-established general practice of 36 years in south Minneapolis with a well equipped office. Must retire because of physical disability. If interested phone 822-0493 after 7:00 P.M. any day, or write MINNESOTA MEDICINE 411; 375 Jackson, St. Paul, Minnesota 55101.

DESIRE TO GIVE away a general surgery practice which should immediately provide a versatile surgeon with 200 majors annually and unlimited ceiling. Will provide modern office facilities in a ten-year-old clinic building and guarantee a minimum income with no strings attached. Should be board qualified and under forty-five. Excellent hospital facilities with resident anesthesiologist and pathologist. Reason:—desire to limit my practice to Urology. Write or call O. K. Behr, M.D., 407 North Broadway, Crookston, Minnesota—Area Code 218-281-3210.

WANTED BY TWO INTERNISTS—a Board Eligible or Board Certified Internist to practice in the Twin City area. Excellent opportunity and early partnership. Write: MINNESOTA MEDICINE-407, 375 Jackson, St. Paul, 55101.

WANTED—Board Certified or eligible Internist to join two established Internists in medium sized, college community in Minnesota lake country. New clinic facilities. Salary negotiable. Write MINNESOTA MEDICINE 409, 375 Jackson, St. Paul 55101.

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WANTED: General practitioner, licensed in Minnesota, for staff at State-operated Ah-gwah-ching Nursing Home, 481 beds, located in the heart of Minnesota's vacationland, on Leech Lake; forty-hour week, annual vacation, sick leave, and other state Civil Service benefits. Retirement benefits: state-paid life insurance, Blue Cross and Blue Shield coverage . . . night and weekend duty on rotation basis. House, including heat, light, telephone provided in addition to salary. Write Ah-gawh-ching Nursing Home, H. M. Williams, M.D., Superintendent, Ah-gwah-ching, Minnesota 56430.

FOR RENT: 14-room deluxe clinic in shopping center—Robbinsdale. 5 min. from Glenwood Hills and No. Memorial Hospitals—3 months rent free—will subdivide—36th Ave. No. and Noble—Noble Drug, JU 8-9449—Ben or Lou.

GENERAL PRACTITIONER WANTED: To associate with Physician-Surgeon in Owatonna, a Southern Minnesota community, 25,000 population. Clinic building 3 years old, with five large treatment rooms, lab., x-ray, central supply, two doctors' offices, pharmacy, and business offices. Located next door to 85 bed City Hospital. Good opportunity for partnership. Contact: O. W. Roberts, M.D., 920 South Cedar Street, Owatonna, Minnesota. Phone 451-4630.

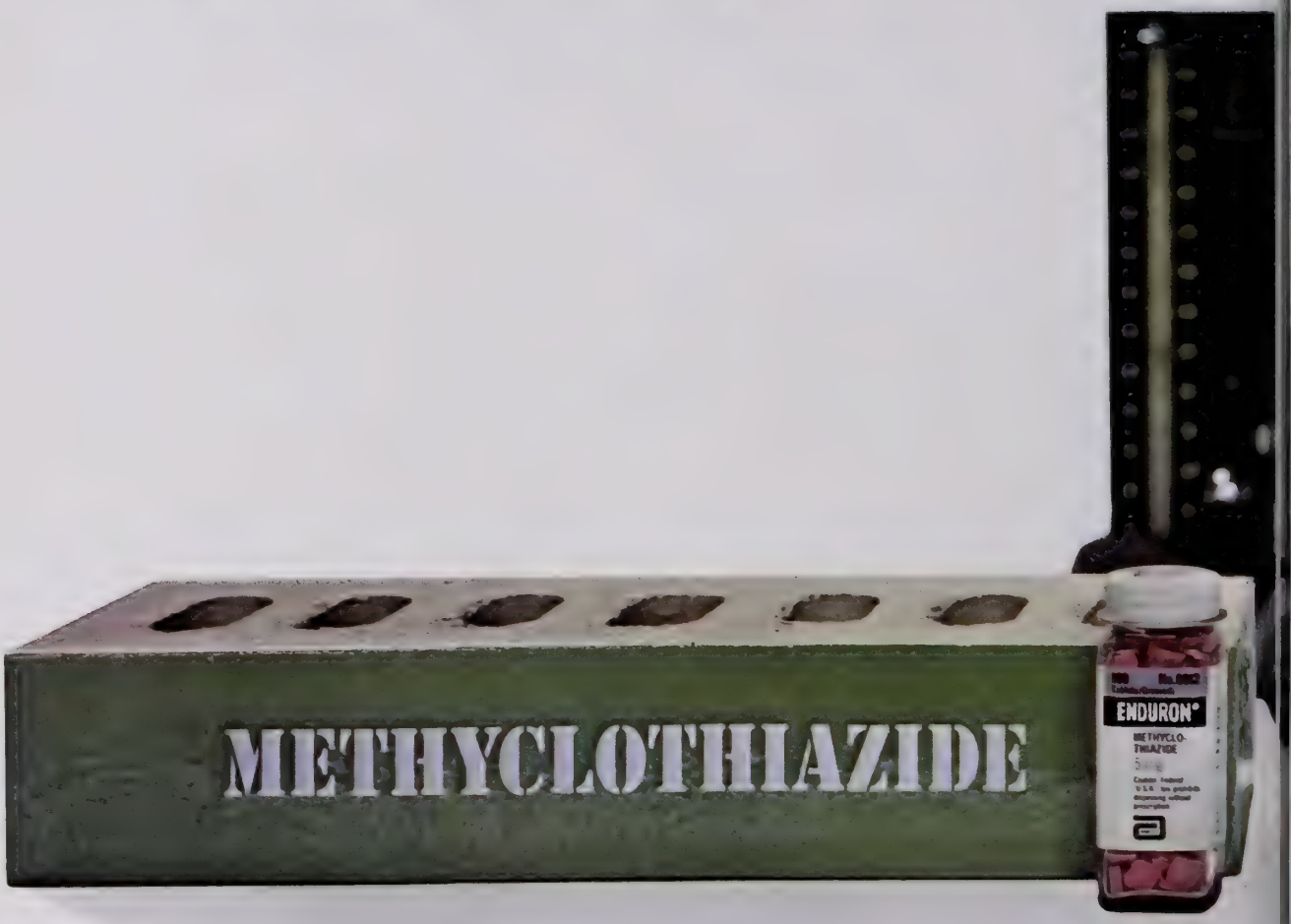
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A simplified approach to the practical management of hypertension



Enduron: (methyclothiazide) A basic building block for mild hypertensives



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Enduron provides an excellent starting therapy. Your patient's sodium excretion is greatly enhanced. Yet potassium loss is low.

The therapeutic action is smooth, and persists for a full 24 hours. With Enduron you can prescribe convenient once-a-day dosage without skimping your patients on day-long thiazide effectiveness.

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Use Enduron as a basic therapy in patients with mild to moderate hypertension. A single 5-mg. tablet each day is ample in most cases.

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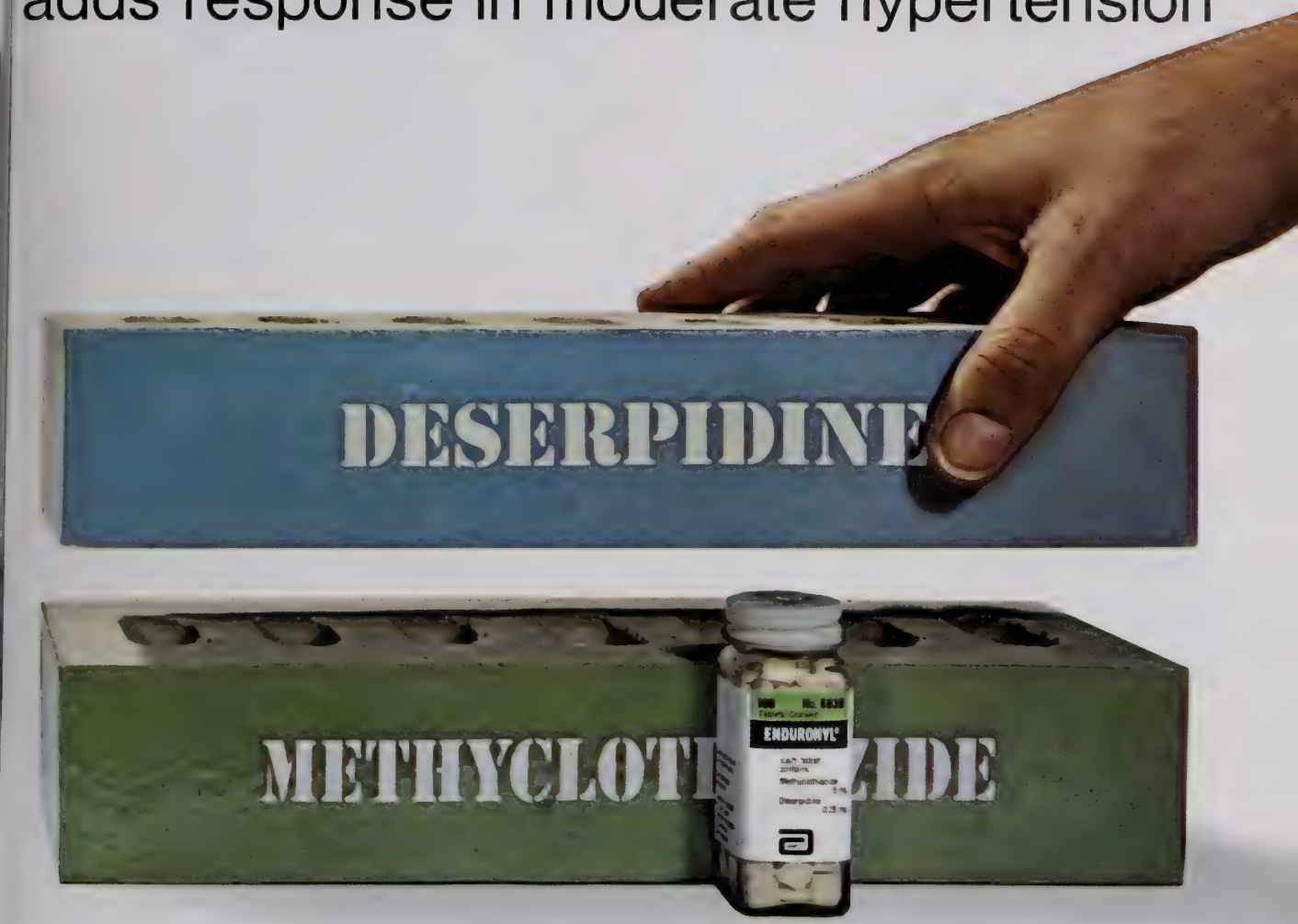
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MILD TO MODERATE TO SEVERE



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Enduronyl: Its deserpidine component adds response in moderate hypertension



Less frequent rauwolfia side effects than with reserpine

When you wish to build further response, consider shifting to Enduronyl.

Enduronyl adds a building block of *deserpidine*. This is a purified rauwolfia alkaloid available only from Abbott. It adds good antihypertensive and tranquilizing activity. Yet its incidence of untoward effects, particularly lethargy and depression, is lower than with reserpine.

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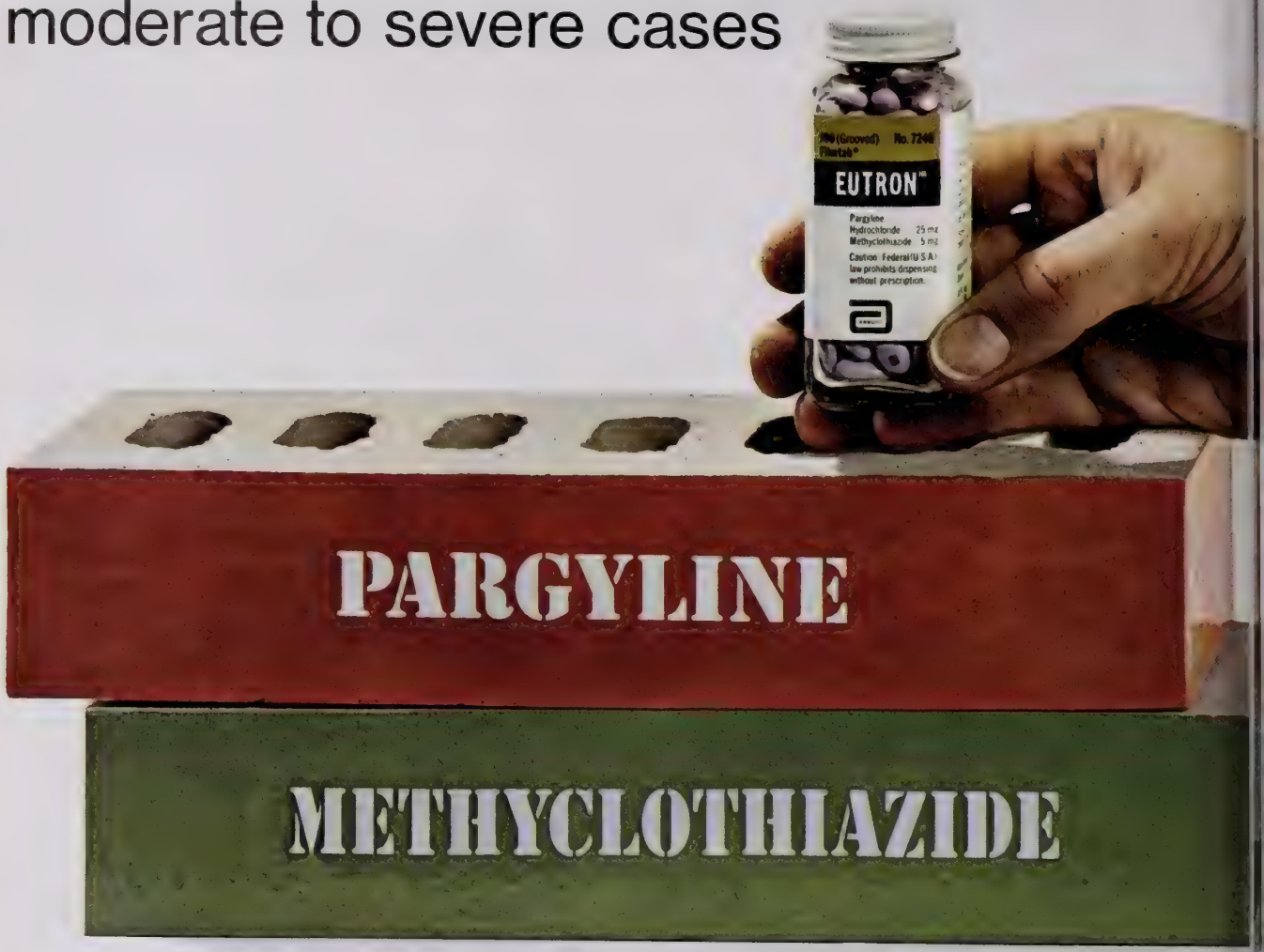
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801094

Eutron: A unique combination for handling moderate to severe cases



Affords almost uniform diastolic reduction in all body positions

Eutron lowers diastolic pressures nearly equally, whether your patient is standing up or lying down.

Thus, in clinical trials, average *standing* diastolic readings were reduced from 112 pre-treatment to 90 post-treatment; *sitting* from 115 to 95; and *recumbent* from 112 to 94.

Note that following Eutron, the diastolic reductions were nearly alike in all three body positions.

Use Eutron for managing your moderate to severe cases. Its building blocks enhance each other; hence lesser doses often suffice.

Once a day, every day

EUTRON™

PARGYLINE HYDROCHLORIDE 25 mg.
with METHYCLOTHIAZIDE 5 mg.

MILD TO MODERATE TO SEVERE



See Brief Summary on final page of advertisement

801094

ENDURON® | ENDURONYL®

METHYCLOTHIAZIDE

Each tablet contains
Methyclothiazide 5 mg. with
Deserpidine 0.25 mg. or 0.5 mg.

Indications: Edema and mild to moderate hypertension (Enduron), and mild to moderately severe hypertension (Enduronyl). More potent agents, if added, can be given at reduced dosage.

Contraindications: Sensitivity to thiazides; severe renal disease (except nephrosis) or shutdown; severe hepatic disease or impending hepatic coma (hepatic coma due to hypokalemia has been reported in patients on thiazides). Do not use Enduronyl in severe mental depression, suicidal tendencies, active peptic ulcer, or ulcerative colitis.

Warnings: Consider possible sensitivity where there is history of allergy or asthma. If added potassium is indicated, dietary supplementation is recommended. Reserve enteric-coated potassium tablets for cautious use only when necessary, as they may induce serious or fatal small bowel lesions (stenosis with or without ulceration), cause obstruction, hemorrhage, and perforation often requiring surgery; discontinue them immediately if abdominal pain, distention, nausea, vomiting, or g.i. bleeding occurs. Neither Enduron nor Enduronyl contains added potassium.

Precautions: Use thiazides cautiously in severe renal dysfunction, impaired hepatic function or progressive liver disease; also in pregnancy (bone marrow depression, thrombocytopenia, and altered carbohydrate metabolism have been reported in certain newborn). In surgery, thiazides may reduce response to vasopressors, and increase response to tubocurarine. Antihypertensive response may be enhanced following sympathectomy. Watch for electrolyte imbalance (e.g., hyponatremia) in all patients. In hypokalemia (especially in digitalized patients) give supplemental potassium. In hypochloremic alkalosis, give supplemental chloride.

Use rauwolfias with caution in patients with history of peptic ulcer. Rauwolfias with anesthetics may produce hypotension and bradycardia. Discontinue Enduronyl two weeks before elective surgery. Consider vagal blocking agents during emergency surgery. In epilepsy, adjust anticonvulsant dosage. In electroshock, shorten stimulus strength and duration. In occasional patients with depressive tendencies, rauwolfias may precipitate severe mental depression that usually disappears when drug is stopped.

Adverse Reactions: Thiazide reaction include blood dyscrasias (thrombocytopenia with purpura, agranulocytosis, aplastic anemia); elevation of BUN, serum uric acid or blood sugar; anorexia, nausea, vomiting, diarrhea, headache, dizziness, paresthesia, weakness, skin rash, photosensitivity, jaundice, symtomatic gout, and pancreatitis. Cutaneous vasculitis in the elderly has been reported with other thiazides. Adverse effects with deserpidine are qualitatively similar to those with reserpine, but their incidence is lower. These include nasal stuffiness, abdominal cramps or diarrhea, nausea, headache, weight gain, reduced libido and potency, peptic ulcer aggravation, epistaxis, skin eruption, asthma in susceptible patients, electrolyte imbalance, excessive salivation, and a reversible Parkinson's syndrome. Excessive drowsiness, fatigue, weakness, and nightmares may signal mental depression. Thrombocytopenia, purpura, and a symptom manifested by dull sensorium, deafness, uveitis, glaucoma, and optic atrophy are rare allergic reactions to other rauwolfias. Hypotension from antihypertensive agents may precipitate angina attacks in susceptible individuals. Usually adverse reactions disappear when drug is withdrawn.

EUTRON™

Each tablet contains
Pargyline Hydrochloride 25 mg.
with Methyclothiazide 5 mg.

Indications—Moderate to severe hypertension.

Contraindications—Pheochromocytoma, paranoid schizophrenia, hyperthyroidism and advanced renal failure. Not recommended in malignant hypertension, children under 12, pregnant patients.

Do not use with: centrally or peripherally acting sympathomimetic drugs; foods high in tyramine (e.g., aged and natural cheeses); parenteral reserpine or guanethidine; imipramine, amitriptyline, desipramine, nortriptyline or their analogues; other monoamine oxidase inhibitors; methyldopa or dopamine; separate Eutron and these agents by two weeks.

Sensitivity to thiazides; severe renal disease (except nephrosis) or shutdown; severe hepatic disease; impending hepatic coma from thiazide-induced hypokalemia.

Warnings—Patients: 1. No other drugs (particularly "cold preparations" and antihistamines), cheese or alcohol without physician's consent. 2. Promptly report orthostatic symptoms, severe headache, other unusual symptoms. 3. Angina pectoris or coronary artery disease patients must not increase physical activity with improved anginal symptoms or well-being.

Physicians: 1. Use antihistamines, hypnotics, sedatives, tranquilizers and narcotics (meperidine contraindicated) cautiously in reduced doses. 2. Stop Eutron two or more weeks before elective surgery; in emergency surgery reduce premedication (narcotics, sedatives, analgesics, etc.) to 1/4 to 1/5; carefully adjust anesthetic dosage to patient response. 3. Use cautiously in advanced renal failure. 4. Pargyline may induce hypoglycemia. 5. Consider possible sensitivity reactions when a history of allergy or asthma is present. 6. If potassium is indicated, dietary supplement is recommended; enteric-coated potassium tablets may induce serious or fatal small bowel lesions (stenosis with or without ulceration), cause obstruction, hemorrhage, and perforation frequently requiring surgery; discontinue medication immediately if abdominal pain, distention, nausea, vomiting or gastrointestinal bleeding occurs; Eutron does not contain added potassium. 7. Possible systemic lupus erythematosus has been reported for thiazides.

Precautions—Pargyline: Use cautiously at reduced dosage: caffeine, alcohol, antihistamines, barbiturates, chloral hydrate, other hypnotics, sedatives, tranquilizers, narcotics. Periodically do urinalyses, blood counts, liver function tests, etc. Use with caution in liver disease. Watch for orthostatic hypotension, especially in impaired circulation (e.g., angina pectoris, coronary artery disease, cerebral arteriosclerosis); also, augmented hypotension in concomitant febrile illnesses. Reduce or discontinue if hypotension is severe. In impaired renal function watch for cumulative drug effects, elevated BUN and other evidence of progressive renal failure; withdraw drug if these persist. In surgery increased central depressant response (hypotension and increased sedative effect) can be controlled by (1) discontinuing at least two weeks prior; (2) in emergency surgery lowering dose of premedication; (3) when necessary, administering a vasopressor. Do not use in hyperactive and hyperexcitable patients. Pargyline may unmask severe psychotic symptoms where emotional problems pre-exist. Use cautiously in Parkinsonism, especially with antiparkinsonian agents. In prolonged therapy, examine for change in color perception, visual fields, fundi and visual acuity. Also, prolonged therapy has made certain patients refractory to nerve blocking effects of local anesthetics.

Methyclothiazide: Use cautiously in severe renal dysfunction, impaired hepatic function or progressive liver disease; also in pregnancy (bone marrow depression, thrombocytopenia, and altered carbohydrate metabolism have been reported in certain newborn). In surgery thiazide may reduce vasopressor response and increase tubocurarine response. Antihypertensive response may be enhanced following sympathectomy. Watch for electrolyte imbalance (e.g., hyponatremia). Give supplemental chloride if hypochloremic alkalosis occurs and supplemental potassium if hypokalemia occurs (especially in digitalized patients). Thiazides may decrease serum P.B.I. without signs of thyroid disturbance.

Adverse Reactions — Pargyline: Orthostatic hypotension and associated symptoms, mild constipation, fluid retention, edema, dry mouth, sweating, increased appetite, arthralgia, nausea, vomiting, headache, insomnia, difficult in micturition, nightmares, impotence, delayed ejaculation, rash, purpura, weight gain, hyperexcitability, increased neuromuscular activity and other extrapyramidal symptoms. Drug fever is extremely rare. Reduction in blood sugar and hypoglycemic effects are possible. Congestive heart failure has been reported in a few patients with reduced cardiac reserve.

Methyclothiazide: Blood dyscrasias (thrombocytopenia with purpura, agranulocytosis, aplastic anemia); elevation of BUN, blood sugar or serum uric acid (gout may be induced); anorexia, nausea, vomiting, diarrhea, headache, dizziness, paresthesia, weakness, skin rash, photosensitivity, jaundice and pancreatitis. Cutaneous vasculitis in elderly patients has been reported with other thiazides.

If side effects are severe or persist, reduce dosage or withdraw drug. 804438R

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Editor's Soliloquy (Continued from Page 1085).

Doctor-Populace Ratio*

Country	Ratio
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Great Britain	1-876
Canada	1-910
Japan	1-930
Sweden	1-1100
Mexico	1-1700
Africa	1-3600
India	1-6000

*Manpower, J Med Educ 41:27, 1966.

References

1. Med J Australia 1:990, 1967.
2. Amer J Surg 114:175, 1967 (East South Central, Kentucky, Tennessee, Mississippi, Alabama).
3. Health of Mankind, Ciba Foundation, Little, Brown & Co., p. 223, 1967.
4. JAMA 198:1100, 1966.
5. Manpower. J Med Educ 41:61, 1966.

Classified Advertisements

(Continued from page 1156)

GENERAL PRACTITIONER: Serve as Medical Director of 50-bed Minnesota State Prison Hospital; staff of registered nurses, surgical nurse, laboratory technician, dentist, and consultants with various specialties; surgical residents provided by University of Minnesota Hospitals; salary $20,800 to $27,800 based on experience and qualifications; benefits include hospitalization and life insurance, vacation and sick leave accruals, liberal retirement program; located in Stillwater, Minnesota, in the recreational St. Croix River Valley; 30 minutes from Minneapolis-St. Paul by freeway. Contact Personnel Department, Box 55, Stillwater, Minnesota 55882.

GENERALIST as member of Medical Staff of progressive State Hospital in Michigan's Vacationland. Hospital has 3-year accreditation. JCAH and 3-year residency accreditation by A.P.A. Salary $17,867.20 to $21,777.60. Excellent fringe benefits. Civil Service security when qualified. Apply L. B. Young, M.D. Director of Medical Services, Traverse City State Hospital, Traverse City, Michigan 49684.

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FOR SALE: 2 exam room units. Also new Cambridge EKG, Hematocrit, and various other equipment. Call Faribault 507—334-7739 or write Dr. A. D. Mattson, 808 Home Place, Faribault. Minn. 55021.

Southern Minnesota Medical Association

The annual convention for the Southern Minnesota Medical Association will be held Friday, September 20, 1968 at the Owatonna Country Club in Owatonna, Minnesota. The program will be published in the September issue of MINNESOTA MEDICINE. Contact: Dr. Robert Conley, Mankato Clinic, Mankato, Minnesota.

Minnesota Medicine at a Glance

Fat Embolism—*Evarts* Page 1035.

Fortunately, fat embolism is not sufficiently frequent to keep it constantly in mind, though it should be one of the concerns of a physician who is seeing patients that have been injured. Ninety percent of the patients with fat embolism demonstrate their symptoms within a period of 48 hours after injury.

The signs, symptoms and treatment of this sequel to trauma are very lucidly demonstrated in Evarts' manuscript.

Myocardial Revascularization Surgery—*Effler* Page 1039.

At the Cleveland Clinic more than 1500 internal mammary artery implant procedures have been performed in the past six years and, as experience has been gained, the procedures used for restoring circulation to the deficiently functioning myocardium have been found to have increasing value. Effler and associates use a combination of the Vineberg and the Sewell procedure. Proof of its value has been established by postoperative internal mammary arteriography, with the best results obtained on those patients who have increasing angina pectoris in which the coronary arteriogram demonstrates almost complete obstruction of the major coronary artery.

Bacterial Infection Emergencies—*McHenry & Van Ommen* Page 1043.

These authors discuss clinical emergencies due to bacterial infection and point out that shock may be associated with bacteremia due to gram-negative bacilli. Other factors causing similar emergent problems are acute bacterial meningitis, fulminating meningococcemia, acute bacterial endocarditis and staphylococcal enterocolitis. The various factors causing these emergent conditions and the management are discussed.

The Cadaver Kidney as a Donor—*Straffon et al.* Page 1049.

One hundred seventeen renal transplants were from cadaver donors. In this group the one-year survival rate was 48%, and two patients have entered their fifth year with a functioning renal allograft from a cadaver donor. These authors consider that renal transplantion along with intermittent hemodialysis must be considered as therapy for the patient with terminal renal failure.

Essential Hypertension—*Vidt & Gifford* Page 1055.

Special attention has been paid to the diastolic blood pressure in hypertension. The authors have outlined therapeutic regimens for complicated and uncomplicated hypertension. They point out that as long as the diastolic blood pressure does not exceed 100 milligrams and the systolic pressure does not exceed 220 milligrams mercury, treatment is probably not necessary unless there is heart failure.

Colonic and Rectal Polyps—*Hawk et al.* Page 1063.

This manuscript deals principally with the symptoms, histopathology and recognition of polyps that are encountered in young individuals. In those polyps under discussion there is very little chance of lethal malignancy occurring; therefore the treatment can in large part be limited to local management. Electrosurgical excision, these authors point out, minimizes the possibility of implantation if the lesion should prove to be malignant.

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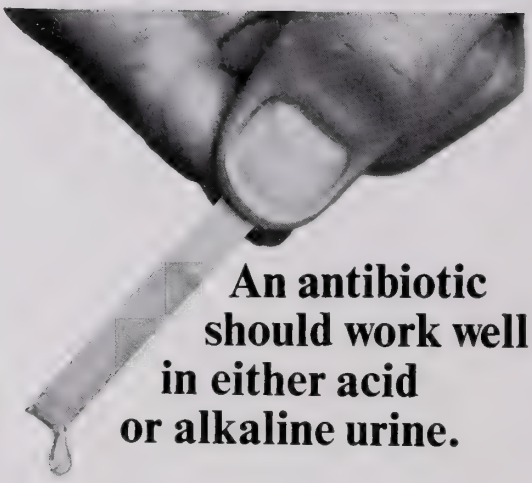


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Effectiveness: DECLOMYCIN Demethylchlortetracycline should be equally or more effective therapeutically than other tetracyclines in infections caused by organisms sensitive to the tetracyclines.

Contraindication: History of hypersensitivity to demethylchlortetracycline.

Warning: In renal impairment, usual doses may lead to excessive accumulation and liver toxicity. Under such conditions, lower than usual doses are indicated, and, if therapy is prolonged, serum level determinations may be advisable. A photodynamic reaction to natural or artificial sunlight has been observed. Small amounts of drug and short exposure may produce an exaggerated sunburn reaction which may range from erythema to severe skin manifestations. In a smaller proportion, photoallergic reactions have been reported. Patients should avoid direct exposure to sunlight and discontinue drug at the first evidence of skin discomfort. Necessary subsequent courses of treatment with tetracyclines should be carefully observed.

Precautions: Overgrowth of nonsusceptible organisms may occur. Constant observation is essential. If new infections appear, appropriate measures should be taken. In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment.

Side Effects: Gastrointestinal system – anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin – maculopapular and erythematous rashes; a rare case of exfoliative dermatitis has been reported. Photosensitivity; onycholysis and discoloration of the nails (rare). Kidney – rise in BUN, apparently dose-related. Transient increase in urinary output, sometimes accompanied by thirst (rare). Hypersensitivity reactions–urticaria, angioneurotic edema, anaphylaxis. Teeth – dental staining (yellow-brown) in children of mothers given this drug during the latter half of pregnancy, and in children given the drug during the neonatal period, infancy and early childhood. Enamel hypoplasia has been seen in a few children. If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy. Demethylchlortetracycline may form a stable calcium complex in any bone-forming tissue with no serious harmful effects reported thus far in humans.

Average Adult Daily Dosage: 150 mg q.i.d. or 300 mg b.i.d. Should be given 1 hour before or 2 hours after meals, since absorption is impaired by the concomitant administration of high calcium content drugs, foods and some dairy products. Treatment of streptococcal infections should continue for 10 days, even though symptoms have subsided.

Capsules: 150 mg; Tablets: film coated – 300 mg, 150 mg and 75 mg of demethylchlortetracycline HCl.

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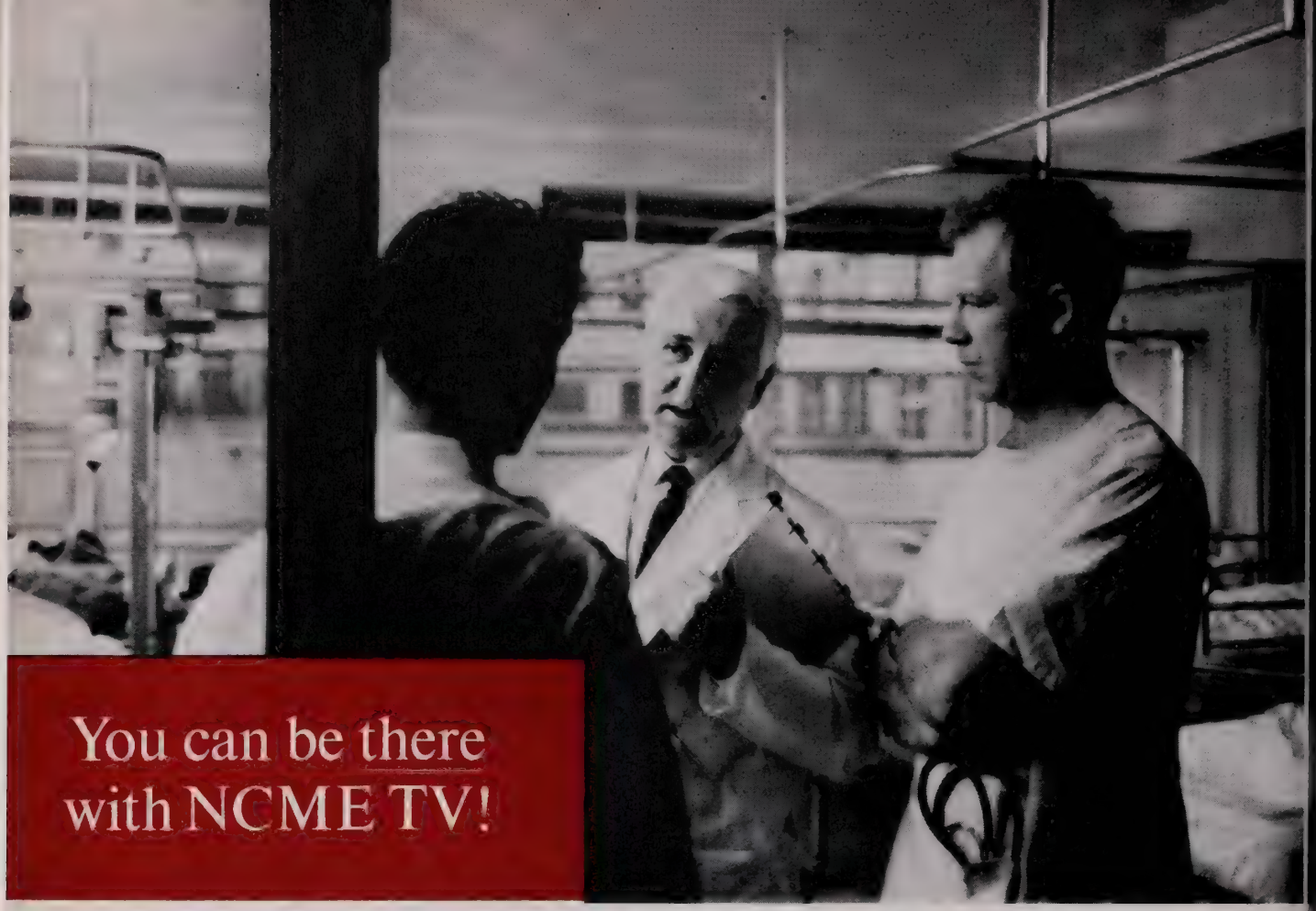
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In this program, Dr. Sawyer performs the operation on a patient with gross occlusion of the right iliac, femoral and popliteal arteries.

In Dr. Sawyer's view, gas endarterectomy has several advantages over mechanical methods: the operation can be completed faster, causes less damage to the arteries and offers a more successful outcome.

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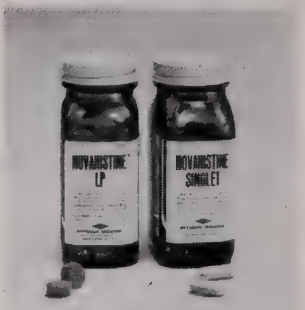
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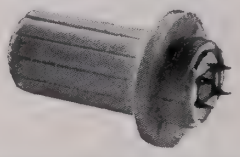
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President's Letter

Otolaryngologists, Let Us Face the Facts!

THERE IS A dire need for ear, nose, and throat specialists all over the country. In our own state of Minnesota, for example, such specialists are concentrated mainly in three cities: Minneapolis, St. Paul, and Rochester. In fact, 30 years ago we had more ear, nose, and throat specialists in the smaller communities than we have today.

The Board of Certification has made great efforts to improve the quality of the specialty by lengthening the training program and providing stricter control of the educational centers. This has provided a trend toward subspecialization and has encouraged congregation in large cities. Somehow, the people living in smaller towns have been forgotten.

In an effort to provide a more even distribution of the specialty, a more flexible training program is urgently needed: that is, a plan for a three-year program in general ear, nose, and throat training. This program could be made more effective by severely reducing the time spent in general surgical training during the internship. Training should be extensive enough, however, so that the graduate student is qualified for board examination. A five-year or even a six-year program should be set up for the more academic and research-oriented students and also for those who elect to enter a subspecialty.

O. Erik Hallberg, M.D.
President
Minnesota Academy of Ophthalmology and Otolaryngology

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Examination of the Comatose Patient*

MILTON ALTER, M.D., Ph.D†
Minneapolis, Minnesota

IN EVALUATING a comatose patient, the physician must have in mind a list of possible causes. The three main causes are oxygen deficiency, substrate deficiency, and enzyme disturbances.

Causes of Coma

Oxygen Deficiency

The brain's metabolism is dependent upon aerobic processes, and it has no storage capacity for oxygen. Deprivation of oxygen, even for a few moments, interferes with the ability of the brain to function and manifests clinically as impaired consciousness. The cause of the oxygen deprivation may be generalized, as encountered in an airplane whose oxygen supply is suddenly lost, in an anemic individual whose blood cannot carry enough oxygen, or in an individual with a myocardial infarction, whose brain is poorly perfused with blood. On the other hand, the oxygen deficit may be localized, as when a vessel in the brain becomes occluded or a major artery is stenotic.

Substrate Deficiency

In the brain, the major metabolite is glucose. For practical purposes the brain utilizes no other substrate. Hence, in the presence of coma, the clinician should examine the glucose level in the blood. Ideally he should examine the glucose available to the central nervous system, since there may be a discrepancy between the blood level of glucose and the amount of glucose on the central nervous system side of the blood-brain barrier. However, as this is seldom practical, a blood sugar must suffice.

Enzyme Disturbance

Enzyme disturbances occur in a number of conditions. Those which should be considered include diabetes, uremia and hepatic failure. Insulin is the enzyme which is deficient in

*Presented at the Continuation Course in Neurological Emergencies sponsored by the University of Minnesota, Minneapolis, November 8, 1967.
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diabetes, and renal failure probably involves impaired function of many enzymes. The specific enzymatic defects in liver failure are not known, but probably ammonia metabolism is involved in some way as ingestion of protein aggravates the mental aberrations when the liver is failing and blood ammonia levels rise.

Ionic disturbances affect enzyme function, at least in part, by interfering with pH. Accumulation of CO_2, for example, may cause a shift toward the acid level in the blood and create a condition in which some enzymes work less efficiently. Accumulation or depletion of water affects the concentration of ions and may produce levels which are detrimental to the function of certain enzymes.

Other Factors

Exogenous factors such as temperature changes and exposure to organic and inorganic toxins affect enzyme function and may impair consciousness. Deficiency or excess of cofactors, such as vitamin B_1, essential for brain metabolism, may likewise interfere with brain function.

Table 1 also lists conditions in which multiple factors are involved in accounting for coma. Trauma is an example in which oxygen may be deficient, cerebral vessels may be torn, and the functions of many enzymes may be disturbed. It should be realized that the factors mentioned in Table 1 represent only a partial list.

In many cases, the cause of the coma will be obvious: for example, trauma to the head. These cases are mainly management problems. However, the cause of the coma is sometimes obscure, and it is worthwhile to examine the experience of Plum and Posner[1] as regards the frequency of various causes of coma in cases referred to them initially as "etiology unknown" (Table 2).

Examination of the Comatose Patient

While history usually suffices to clarify the etiology of coma, the examination will indicate where the lesion is. Of course, the evaluation must be thorough, but often the patient's precarious state hardly allows a leisurely work-up. It is important, therefore, to concentrate on those aspects of the examination which are likely to be most informative as to site of the pathology. There are a number of questions which the physician must keep in mind when making his evaluation of the patient in coma.

What is the Level of Consciousness?

An *alert* patient responds fully, immediately, and appropriately to stimuli. A *lethargic* patient is drowsy, indifferent and slow and gives incomplete responses. *Obtundation* is characterized by duller indifference with wakefulness barely maintained, while a *stuporous* patient can be roused only by strong stimuli. *Moderately deep coma* is present when only rudi-

TABLE 1
Causes of Coma

1. O_2 deficiency		
A. *Generalized:*	hypoxia, hypoxemia, hemodynamic	
B. *Localized:*	cerebrovascular insufficiency, aortocranial vascular insufficiency	
2. Substrate deficiency		
A. *Hypoglycemia*		
3. Enzyme disturbance		
A. *Endogenous:*	diabetic, uremic, hepatic	
B. *Ionic*	$CO_2 \uparrow\downarrow$, $H_2O \uparrow\downarrow$	
C. *Exogenous:*	temperature—$\uparrow\downarrow$	
	chemical	
	a. inorganic:	heavy metals (Pb, As, Hg, Au, Mg, etc.) halogens
	b. organic:	hypnotics, sedatives, narcotics, tranquilizers, alcohol
	c. essential cofactors:	vitamins, minerals
4. Multiple		
A. *Seizures*	D. *Trauma*	
B. *Increased cranial pressure*	E. *Infection*	
C. *Tumors*	F. *Valsalva syncope*	
	G. *Cholinesterase inhibitors*	

TABLE 2
CAUSES OF COMA IN CASES INITIALLY REFERRED AS "ETIOLOGY UNKNOWN"

Cause	Number
1. Toxins and deficiencies	180
2. Hemorrhages	77
3. Anoxia and ischemia	51
4. Infarction	42
5. Infection	16
6. Trauma	9
7. Tumors	7
8. Psychiatric	4
Total	386

mentary reflex responses to strong stimuli occur, e.g., withdrawal, sucking, chewing, swallowing. With *deep coma* no motor responses occur even to strong stimuli. It is well to remember that agitation, confusion, disorientation, inattention, delirium and misperception (illusions and hallucinations) are signs of impending coma.

How is the Patient Breathing?

Posthyperventilation apnea consists of persistent apnea (>12 secs.) after hyperventilation. The mechanism is not clear in all its details, but depressed consciousness, usually from bilateral hemispheric disturbance, is thought to interfere with central (forebrain) control of the response to pCO_2. In posthyperventilation apnea, the respirations stop when deep breathing has lowered pCO_2 to 8-14 mm Hg. Normally, rising pCO_2 triggers breathing within 10 seconds. In abnormal subjects, apnea may persist 12 to 30 seconds or more after hyperventilation.

In Cheyne-Stokes respirations, hyperpnea alternates with apnea periodically. This breathing pattern suggests damage in deep portions of cerebral hemispheres and basal ganglia with involvement of the internal capsule. It may indicate impending herniation. It represents an abnormally increased response to pCO_2 and decreased sensitivity of the forebrain to ventilatory stimuli.

Central neurogenic hyperventilation is characterized by regular, rapid, deep respirations and usually occurs with a lesion in the tegmentum from the lower part of the midbrain down to the lower pons. It is often caused by blood irritating reticular gray matter around the Sylvian aqueduct and fourth ventricle. It produces respiratory alkalosis and is not modified by administration of O_2.

Apneustic breathing* consists of a prolonged inspiratory cramp followed by expiration and is produced by a lesion affecting the dorsolateral part of the tegmentum and dorsal pontine nuclei, e.g., thrombosis of a branch of the basilar artery. It is usually not seen with herniation, as the latter tends to produce medial brain stem lesions.

Cluster breathing occurs with high medullary lesions and is characterized by a burst of rapid irregular respirations followed by irregular shallow breathing or apnea. Duration of the interval between rapid and slow breathing may be irregular. Sometimes very deep gasps occur, usually before respirations cease altogether and death supervenes.

Ataxic breathing is a completely irregular pattern with deep and shallow breaths occurring randomly. The rate is slow. This type of breathing is caused by lesions which disrupt reciprocal pathways between inspiratory and expiratory neurons in the medulla. In this state, depressant drug hypersensitivity exists and a sedative may produce apnea. Hence, when this breathing pattern is noted, one must be extremely cautious with use of sedatives and analgesics which depress respiration.

What is the Size and Reactivity of the Pupils?

Pupillary size depends on both sympathetic and parasympathetic influences. The anatomy of the autonomic pathways may be summarized as follows: The *sympathetic* pathway sequentially traverses the hypothalamus—tegmentum—thoracolumbar spinal cord—sympathetic rami—sympathetic ganglia—sympathetic chain—ciliary ganglion (without synapse) to end in the radial fibers of the pupil. Pupillary dilatation (mydriasis) results.

The *parasympathetic* pathway may be traced from the pretectal nuclei—Edinger-Westphal nucleus—III nerve—to the ciliary ganglion where a synapse occurs. Thence, the postganglionic fiber passes on to the circular fibers of the pupil and causes pupillary constriction

†See Test Your Word Score Page 1213.

TABLE 3
PUPILLARY FINDINGS OF LOCALIZING SIGNIFICANCE

Site of lesion	Pupillary findings
1. cerebrum	non-specific
2. hypothalamus	constricted
3. midbrain	
a. pretectum	light reflex negative; ciliospinal reflex positive
b. nuclei	negative to all stimuli
c. III nerve	dilated pupil fixed to light directly and consensually; ciliospinal positive opposite side
4. pons	constricted (pin-point constriction means brain-stem hemorrhage)
5. lateral medulla	Horner's; light reflex positive
6. peripheral III	dilated (may be compressed against tentorium or posterior cerebral artery)

Note: If neck flexion gives dilatation of pupils suspect impending herniation.

(miosis).

Reflexes of clinical importance which involve the pupil consist of the light reflex and the ciliospinal reflex. The pathway of the *light reflex* involves optic nerve—optic tract—diencephalic pretectum—Edinger-Westphal nucleus bilaterally—III nerve—ciliary ganglion—to the circular fibers of the pupil. Miosis is produced on the ipsilateral and contralateral sides (direct and consensual reflex).

The *ciliospinal reflex* consists of an ipsilateral dilatation of the pupil to a noxious stimulus. Its anatomy involves a direct pathway from hypothalamus to the sympathetic system which causes active mydriasis and an indirect pathway which passes up the midbrain to inhibit the Edinger-Westphal nucleus. The ciliospinal reflex disappears with brain stem damage. Pupillary findings of localizing significance are listed in Table 3.

It is helpful to be aware of the effects of various drugs on the pupillary responses. Atropine causes dilatation by blocking parasympathetic influence. The block allows sympathetics to take over and dilatation of the pupils results. Pilocarpine is a parasympathomimetic drug and hence causes constriction like parasympathetic stimulation. Doriden (glutethimide) results in pupils which are fixed to light, irregular, and unequal. Opiates produce pin-point pupils, but bright light may still induce a pupillary response. Anoxia causes dilatation of the pupils.

How Do the Eyes Move?

Conjugate eye movements depend on complex interactions among 12 eye muscles. The movement of each eye in a particular direction is controlled by a pair of muscles. For example, abduction of the right eye involves contraction by the right lateral rectus and relaxation of the right medial rectus. The action of the superior and inferior recti and the superior and inferior oblique muscles may be thought of as stabilizers during abduction; they are certainly not passive. A thorough understanding of how the eye muscles work is essential to an understanding of eye movements. Here, however, the neurological control mechanisms will be emphasized.

One supranuclear control mechanism involves the frontal cortex (area 8) and is concerned with voluntary eye movements. Another involves the occipital cortex and subserves visual fixation. A third is believed to be centered in the parietotemporal region and controls opticokinetic movements. An internuclear mechanism exists which coordinates the conjugate movements of the eyes. It involves the medial longitudinal fasciculus. A vestibular contribution to eye control is derived from receptors in the semicircular canals which detect rotation, acceleration and deceleration. The fastigial nuclei of the cerebellum also serve to modulate eye movement. Finally, proprioceptors from neck muscles influence eye movements and account for the oculocephalic reflex about which more will be said later.

In order to evaluate extraocular movements, note should be taken first of the resting position of the eyes. Normally the eyes should be in a neutral position. Use of the light reflected from the cornea helps detect the presence of strabismus. If the head is rotated rapidly, the eyes seem to lag behind and deviate in a direction opposite to the head movement, like a doll's. The "doll's eye phenomenon" is not elicited in the normal individual. It constitutes the oculocephalic reflex.

Caloric stimulation also causes the eyes to deviate. Ice water may be instilled into the external ear after checking the intactness of the tympanic membrane and cleaning out cerumen. If the patient is supine, the head is tilted 30 degrees forward. If the patient is in the sitting position, the head is tilted 60 degrees backward. These positions will bring the lateral semicircular canal into vertical alignment and permit convection currents induced by the cold water instillation to stimulate the labyrinth.

Localization of lesions using eye movements are summarized in Table 4.

Eyes in the neutral position have no localizing value. With conjugate horizontal deviation, the lesion is usually in the cerebral hemisphere toward which the eyes deviate. The patient is "looking at the lesion." This holds true if the eyes are fully deviated and the doll's head maneuver yields deviation beyond the midline. However, if the eyes are only partially deviated, and head rotation fails to cause deviation beyond the midline, then the lesion is in the brain stem on the side opposite the direction of the deviation. The patient is

"looking away from the lesion." With conjugate downward deviation, the lesion is causing mesencephalic compression (setting sun sign), or there is mesencephalic metabolic depression. If the doll's eye maneuver produced by tilting the head downward produces deviation above the midline, then the lesion is metabolic. If eye deviation in response to head tilting is incomplete, then the lesion is anatomic.

What Movements Occur in the Limbs and Trunk?

Gegenhalten (paratonic resistance) consists of passive, plastic-like resistance of the extremities. The examiner has the impression that the patient is not cooperating. A grasp reflex and a positive Babinski may be found on the side of the lesion. This movement abnormality may be caused by a lesion in the frontal lobes. It is an early sign and may indicate the presence of diffuse vascular disease, metabolic disease, or a tumor.

The *response of the limb to noxious stimuli* is important. The response may be an appropriate withdrawal, which indicates that sensory pathways and motor pathways are at least partially intact. If the response to noxious stimuli is absent on one side, it indicates destruction of the corticospinal system or the spinothalamic system on that side. If bilaterally absent, deep coma, bilateral corticospinal damage, or a pontomedullary lesion should be suspected. If the response to noxious stimuli is inappropriate, one may see decorticate or decerebrate rigidity rather than appropriate withdrawal.

Decorticate rigidity may be recognized by the following features: the upper limb shows adduction with flexion at the elbow, wrist, and fingers. The lower limb is held in extension and is usually internally rotated with feet in plantar flexion. Decorticate rigidity results from damage to a frontal lobe or the thalamus.

Decerebrate rigidity consists of opisthotonus, clenched teeth, extended, adducted and hyperpronated arms with extended legs, and feet in plantar flexion. Experimentally, decerebrate rigidity is associated with lesions in the midpons which spare the vestibular nuclei and

TABLE 4
EYE POSITION AND MOVEMENTS RELATED TO SITE OF LESION

State	Eye Position	Involuntary Eye Movement	Oculocephalic Reflex	Response to Caloric Stimulation
1. Awake—no lesion	neutral	none	none	nystagmus
2. Bilateral cerebral	neutral	none	brisk	sustained deviation
3. Frontal				
a. destructive	deviated to side of lesion (non-hemiparetic side)	occasionally, nystagmus	hypoactive	hypoactive
b. irritative	away from side of lesion	nystagmus away	hypoactive	hypoactive
4. Diffuse, e.g. (Metabolic coma)				
a. light	roving	roving	brisk	brisk
b. deep	fixed	none	absent	absent
5. Medial longitudinal fasciculus	neutral sometimes, skew	none	ipsilateral eye fails to adduct when other eye abducts	ipsilateral eye fails to adduct when other eye abducts
6. Lateral pons	conjugate deviation away from lesion	none	absent when head rotated to side of lesion	absent on side of lesion
7. Dorsolateral pons	skew deviation	none	may be absent or dysconjugate	may be absent or dysconjugate
8. Mesencephalic tegmentum	neutral or converged	retraction bobbing	present	present
9. Third ventricle	variable	see-saw	present	present

TABLE 5
CENTRAL SYNDROME
Early Diencephalic

1.	Consciousness	drowsy or agitated
2.	Respirations	pauses, sighs, yawns
3.	Pupils	small but reactive
4.	Ciliospinal reflex	present
5.	Oculocephalic reflex	brisk
6.	Oculovestibular reflex	conjugate deviation
7.	Movements	appropriate or decorticate contralateral Babinski ipsilateral gegenhalten

TABLE 6
CENTRAL SYNDROME
Late Diencephalic

1.	Consciousness	stuporous
2.	Respirations	Cheyne-Stokes
3.	Pupils	small but reactive
4.	Ciliospinal reflex	present
5.	Oculocephalic reflex	brisk
6.	Oculovestibular reflex	conjugate deviation
7.	Movements	grasp reflex contralateral decerebrate rigidity ipsilateral decorticate response bilateral Babinski

TABLE 7
CENTRAL SYNDROME
Midbrain & Upper Pons

1.	Consciousness	comatose
2.	Respirations	Cheyne-Stokes or central hyperventilation
3.	Pupils	dilated, unreactive
4.	Ciliospinal reflex	lost
5.	Oculocephalic reflex	incomplete, sluggish
6.	Oculovestibular reflex	partial, dysconjugate eye movements abducting eye moves better
7.	Movements	decerebrate rigidity

TABLE 8
CENTRAL SYNDROME
Lower Pons & Upper Medulla

1.	Consciousness	deeply comatose
2.	Respirations	rapid and shallow or irregular
3.	Pupils	dilated, unreactive
4.	Ciliospinal reflex	absent
5.	Oculocephalic reflex	absent
6.	Oculovestibular reflex	absent
7.	Movements	none or decerebrate rigidity to strong stimulus

adjacent pontine reticular formation.

Syndromes of Progressive Impairment

Two clinically distinct syndromes of progressive impairment of consciousness have been recognized by Plum and Posner.[1] The first reflects bilateral progressive impairment of the diencephalon and brain stem and is called the *central syndrome*. The second is due to third nerve and lateral midbrain compression and is called the *uncal syndrome*.

Central Syndrome

The central syndrome is more common (Tables 5 through 8). In its early stages, consciousness is impaired. The patient is restless or somnolent. Respirations are interrupted by yawns, sighs and pauses but are otherwise regular. The doll's head maneuver elicits brisk eye movements which are not seen in a fully alert patient. Caloric stimulation produces conjugate deviation of the eyes, and limb movements may be appropriate, or gegenhalten is present on the ipsilateral side.

At a lower stage of diencephalic function, the patient is stuporous. Cheyne-Stokes respirations are present. The pupils are small but reactive. The ciliospinal reflex is present and the oculocephalic reflex is brisk. The installation of cold water into the ear produces conjugate deviation of the eyes, and movements of the limbs may be impaired. A grasp reflex may be elicited or contralateral decerebrate rigidity may be found. Ipsilaterally, there is a decorticate response, and a bilateral Babinski response may be present.

With involvement of the midbrain and upper pons the patient lapses into coma. Respirations may still be of the Cheyne-Stokes variety or central hyperventilation may be present. The pupils are dilated and unreactive. The ciliospinal reflex is lost. The oculocephalic reflex may be incomplete and sluggish, and the oculovestibular reflex elicits only partial eye deviation. Disconjugate eye movements may be noted, and the abducting eye moves better than the adducting eye. Decerebrate rigidity of the limbs is present.

At still lower levels of involvement of the brain stem involving pons and upper medulla, the patient is deeply comatose. Respirations are rapid and shallow or irregular. The pupils are dilated and unreactive. Ciliospinal, oculo-

TABLE 9
UNCAL SYNDROME

	Early	Late
1. Consciousness	alert	comatose
2. Respirations	normal	irregular, Cheyne-Stokes or central hyperventilation
3. Pupils:		
size	anisocoria	dilated ipsilaterally
reaction	sluggish ipsilaterally	absent ipsilaterally
4. Ciliospinal reflex	present	absent
5. Oculocephalic reflex	present	absent ipsilaterally
6. Oculovestibular	present or impaired ipsilaterally	absent ipsilaterally
7. Movements	ipsilateral hemiplegia (Kernohan's notch)	bilateral Babinski decerebrate rigidity

cephalic, and oculovestibular reflexes are absent. There are no spontaneous movements, but strong stimuli may elicit decerebrate rigidity.

Uncal Syndrome

The uncal syndrome is caused by herniation of the medial portion of the temporal lobe over the free edge of the tentorium. This movement of the temporal lobe often causes compression of the brain stem and may result in a bypass of the progressive stages of the central syndrome.

In the early stages of the uncal syndrome, the patient is quite alert and respirations are normal (Table 9). Anisocoria is a key sign and pupillary dilatation may be evident on the ipsilateral side. Occasionally the ipsilateral pupil is smaller than the contralateral pupil, perhaps because of irritation of the third nerve. The reaction to light on the ipsilateral side may be sluggish. Ciliospinal, oculocephalic, and oculovestibular reflexes are intact although they may be impaired on the ipsilateral side. One may occasionally find ipsilateral hemiplegia because a shift of the brain stem brings the contralateral pyramid up against the tentorium. Since at this point the pyramid has not yet decussated, hemiplegia is found on the ipsilateral side (Kernohan's notch phenomenon).

The patient may pass rapidly from the early to the late uncal stage. He may suddenly become comatose. Respirations may be irregular or central hyperventilation may be found. Occasionally, respirations are of the Cheyne-Stokes variety. The ipsilateral pupil is dilated and does not react to light. Ciliospinal, oculocephalic and oculovestibular reflexes are active ipsilaterally. Bilateral Babinski signs are elicited and there may be decerebrate rigidity.

It is very important to recognize the uncal syndrome in its early stages and institute therapeutic measures at this time. Prognosis is very poor in the late stage of the uncal syndrome.

Summary

Examination of a comatose patient requires a frame of reference regarding common etiologies. These include: impairment of oxygen supply to the brain, impairment of glucose supply, enzyme disturbances, and multiple etiologies. In examining the comatose patient, special attention should be paid to the level of consciousness, the respirations, the pupillary responses, the eye movements and the motor phenomena. A schema for recognizing the stage of coma using these parameters is provided and differences between the central and uncal syndromes are discussed. Familiarity with the points stressed here should help the clinician in managing the comatose patient.

Reference

1. Plum, Fred and Posner, Jerome B.: Diagnosis of Stupor and Coma. F. A. Davis Company, Philadelphia, 1966.

The average man's judgment is so poor, he runs a risk every time he uses it.
—Ed Howe

Osteomyelitis Infection

In my early days with Doc another case came along which taxed my faith in him to the utmost, and eventually proved him to be more right than he knew.

Jake Wirt was a farmer, in his early thirties, living on the outskirts of a tiny village. While he was fixing a ridge on a silo he slipped and fell to the ground, smashing the distal bones of one leg into several fragments, some of which pierced the skin and caused an angry-looking gash. A neighborhood doctor who was called in put the injured leg up in the usual box without ends, and traction pully weights at the foot of the bed. A week elapsed before we were asked, in consultation, to see the leg. The dressing on the wound had not been changed, and Jake was very ill. I was asked to remove the dressing. The odor was almost unbearable.

I lifted off the last piece of gauze very carefully, and there lay before me a sight which both shocked and frightened me. The whole exposed, deeply lacerated surface, about the size of a dollar bill, was alive with squirming, wiggly, juicy maggots!

"Quick!" I cried, "hand me that ether out of my bag and get hot water, soap, and a brush ready. This is unthinkable. Why was this allowed to occur?"

As I prepared to clean up the mess, Doc stepped forward and said calmly, "Wait a minute, Son. Don't get nervous over a few maggots; and don't disturb them until we figure out the reason why they are there."

I stood dumbfounded. If it had not been for the many times he had spiked my medical guns, I would have considered him out of his mind.

In his deliberate, pensive manner, he went on: "Maggots are harmless. Deadly bugs that can destroy bone can destroy life. If the bugs conquer the maggots, the patient will die. If the maggots conquer the bugs, the patient will live. Leave the maggots to their destruction, or to their victory."

I was incredulous. "You think the maggots will eat up the infective germs and clean the wound?"

"That's right. The survival of the fittest."

I was not at all convinced, and thought I should have to sign Jake's death certificate in twenty-four hours. Doc took pity on my consternation, and sympathetically assured me that he would take all responsibility for the young man's life and leg, and suggested that I wait a while before I adversely criticised the incomparable defense forces of Nature.

"And don't think I'm gambling with a man's life, Son. Maggots have saved a lot of legs for me, and they will for you."

Old Doc took care of Jake. Months went by, and the leg was never discussed. One day Doc, with a sly look in his eye, said, "You recall Jake Wirt with the leg?"

"Yes," I said, impertinently, "When did you bury him?"

He laughed heartily. "Don't be too hard on the maggots. Jake will be in tomorrow, and I want you to graft a little skin on a small area that won't heal."

The next day I was speechless when Jake walked in, as normal as anyone. His leg had united firmly, and a square inch of added skin made a complete cure.

Twenty years later the cure of osteomyelitis by maggots was reported in medical literature.*

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*Joseph A. Jerger, M.D.: Doctor—Here's Your Hat! 1939.

Vertebral–Basilar Insufficiency*

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CENTRAL NERVOUS SYSTEM disorders due to cerebrovascular disease may conveniently be classified into those related to either the internal carotid arterial system or the vertebral-basilar arterial system. In either system, cerebrovascular syndromes of the atherosclerotic-thromboembolic type may present as:

(1) transient ischemic episodes,
(2) progressive strokes, and
(3) completed strokes.

This paper will be limited to a discussion of "vertebral-basilar insufficiency." The term refers to the mechanism of production of transient ischemic episodes in the vertebral-basilar system.

During the late 19th and early 20th centuries, a plethora of brainstem and cerebellar vascular syndromes (Wallenberg,‡ Weber's, Millard-Gubler syndromes, etc.) were described. These have most recently been organized and classified by Fisher.[1] In general, it was felt that these characteristic clinical syndromes were due to thrombotic occlusion of specific arteries, e.g., the posterior inferior cerebellar artery, etc. These reports led to a thorough study of brain-stem vascular anatomy and to pathological-clinical correlations of specific lesions.

Kubik and Adams[2] in 1946 emphasized that many of their patients with basilar artery occlusion had experienced transient symptoms, probably related to narrowing of the basilar artery, which could be recognized long before the final fatal occlusive event.

Further observations by Denny-Brown in 1953,[3] and Millikan and Siekert in 1955[4] led to the concept of "intermittent insufficiency of the basilar arterial system." This concept carries with it the implication of transient and intermittent symptomatology related to dynamic changes in blood flow in the vertebral-basilar arterial system.

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‡See page 1244.

Incidence

In the past decade it has become increasingly obvious that this syndrome is indeed very common. Approximately five to 10 per cent of all patients with clinical cerebrovascular disease will have symptoms primarily of vertebral-basilar insufficiency. It is seen at least as frequently as carotid insufficiency. In at least 50 per cent of patients with completed stroke syndromes of the vertebral-basilar type, a history of episodic vertebral-basilar insufficiency preceding the completed stroke may be elicited.

The frequency with which patients manifesting symptoms of vertebral-basilar insufficiency develop completed stroke syndromes (catastrophic or less severe) is unknown. Earlier reports placed the incidence of subsequent infarction in patients with insufficiency as high as 50 per cent. More recent studies by Marshall in 1964[5] suggest that only five to 10 per cent of patients with vertebral-basilar insufficiency eventually develop completed stroke syndromes in the same arterial distribution. However, it is the impression of many clinicians that the latter figure is too low. At any rate, patients with symptoms of vertebral-basilar insufficiency often develop subsequent completed stroke syndromes, usually involving the same central nervous system structures as were affected during the episodes of insufficiency.

Circulatory Factors

Dynamic alterations in cerebral blood flow and perfusion of central nervous system tissue by blood are felt to be directly responsible for the production of episodic neurological dysfunction in these structures. If the period of relative ischemia (or hypoxia) is brief (seconds to several minutes), function may return quickly and completely. If more prolonged ischemia occurs, infarction will usually result.

Anatomical variations in the vertebral and basilar arteries and their branches occur fairly frequently. The right and left vertebral arteries usually arise as the first major branches of the proximal subclavian arteries. In about five per cent of individuals the left vertebral artery arises directly from the arch of the aorta. The two vertebral arteries are frequently of unequal calibre, and occasionally one vertebral artery may be a very slender thread-like vessel. The vertebral arteries ascend through foramina within the transverse processes of the upper six cervical vertebrae, enter the intracranial cavity through the foramen magnum along the anterior aspect of the medulla and, at the level of the upper medulla or lower pons, unite to form the basilar artery. The basilar artery in turn lies along the anterior surface of the pons and, at the junction of pons and mid-brain, it divides into the right and left posterior cerebral arteries. The proximal posterior cerebral arteries are connected to the internal carotid arteries by the posterior communicating arteries, thus completing the posterior half of the "circle of Willis." The posterior communicating arteries are often very small or thread-like. In about 15 per cent of individuals the posterior communicating on at least one side is very large and represents the major source of blood flow to the corresponding posterior cerebral artery.

Under normal circumstances there is thought to be virtually no cross-circulation between the basilar and carotid arterial systems. It can be appreciated that localized obstructions to flow in the various vessels feeding the circle of Willis may lead to changes in the dynamics of flow in the circle.

Each of the major arteries and their branches supply a fairly consistent portion of the brain stem, cerebellum, and posterior cerebral hemispheres (Table 2).

Aside from the circle of Willis, other sites of potential or actual anastomosis are present within the vertebral-basilar system or between this system and the carotid arterial system. These anastomoses are located between the following vessels:

(a) Superior thyroid artery (branch of external carotid) and muscular branches of vertebral arteries in the neck.

(b) Anterior spinal artery and medullary radicals of the segmental vertebral branches.

(c) Occipital artery (external carotid

branch) and muscular branches of vertebral arteries.

(d) Superior cerebellar and posterior inferior cerebellar arteries.

(e) Temporal branches of middle cerebral and posterior cerebral arteries.

(f) Anterior cerebral and occipital branches of posterior cerebral arteries.

(g) Anterior and posterior choroidal arteries.

(h) Internal carotid and basilar arteries via occasional primitive trigeminal and hypoglossal arteries.

It is estimated that approximately 10 per cent of total cerebral blood flow occurs via the vertebral arteries under normal circumstances. However, quantitative measurements of flow in the vertebral-basilar system in any given individual are performed with great difficulty, and the circulatory effects of vascular occlusion at any point in the posterior circulation are quite impossible to predict. It is also quite possible that flow in the vertebral-basilar system may be more directly related to systemic blood pressure and less influenced by arterial pH and pCO_2 than is flow in the carotid arterial system.

Etiological Factors

The most important etiologic factors (Table 1), in terms of frequency of occurrence, are those causing reduction in size of the lumen of the vertebral or basilar arteries, or reduction in systemic blood pressure and cardiac output.

Related to Blood Vessel Wall or Lumen

Atherosclerosis of both the extracranial vertebral arteries and of the intracranial vertebral-basilar system and its branches is by far the most common cause of luminal encroachment. Sites of predilection for the formation of atherosclerotic plaques are located at the origin of the vertebral arteries, at the sites of entry of the vertebral arteries into the vertebral foramina and into the subarachnoid space, at the junction of the vertebral arteries to form the basilar artery, in the upper basilar artery and its bifurcation, and along the proximal portions of the posterior cerebral arteries. Smaller branches are less often the site of atherosclerotic plaques. The resulting pattern of narrowing and occlusion of these arteries may thus be very complex. In addition, atherosclerotic narrowing of the proximal subclavian arteries before the origin of the vertebral arteries may also cause decreased or even reversed flow in the vertebral arteries. This syndrome of "subclavian steal" will be discussed later.

Less common causes of vertebral artery narrowing, usually by external compression, are also listed in Table 1. It is felt that cervical *spondylosis with osteoarthritic compression* of the vertebral arteries in the neck may be a significant factor in many patients whose symptoms are precipitated by neck movements. The other causes listed have been implicated in individual cases. The significance of compression of the arteries in the neck by fibrous or muscular bands is open to question, as is the significance of excessive kinking or loops in the vertebral arteries.

Intermittent *decrease in collateral blood flow* through any of the multiple anastomotic channels could produce transient ischemia in the presence of a fixed stenotic lesion in the vertebral-basilar system. It has been postulated that *embolization* from adherent thrombi located in the proximal vertebral arteries, especially in the neck, may well be one of the most common causes of transient ischemic episodes. Although pathological proof of this postulate

TABLE 1

Etiological Factors In Vertebral-Basilar Insufficiency

A. *Related to Blood Vessel Wall or Lumen:*
Atherosclerosis:
with or without thrombosis or embolization.
Compression of vertebral artery:
cervical spondylosis
acute cervical spine injury
atlanto-axial dislocation
cervical spine manipulation or hyperextension
Klippel-Feil, platybasia or basilar impression syndromes
fibrous bands or muscles?
kinking or loops?
angiography
B. *Related to Blood Pressure:*
Hypotension:
postural
drug induced
blood loss, etc.
cardiac origin
C. *Related to Blood:*
severe anemia
polycythemia
D. *Other:*
chronic or acute pulmonary disease
hypoglycemia

is lacking, it is certainly a very strong possibility. The analogous production of "amaurosis fugax" (intermittent monocular visual loss) in internal carotid artery stenosis is almost certainly due to embolization in many instances.

Related to Blood Pressure

Under normal circumstances the total and regional cerebral blood flow remains remarkably constant despite marked fluctuations in the systemic blood pressure. However, it has been frequently observed that patients may develop symptoms of vertebral-basilar insufficiency under circumstances of hypotension or decreased cardiac output due to a variety of causes. Drug-induced relative hypotension, often during the course of treatment of mild to moderate hypertension, is a common cause. Intermittent decrease in cardiac output, possibly due to transient arrhythmias or myocardial ischemia is frequently implicated.

Changes in the blood, such as decreased oxygen-carrying capacity (severe anemia) and increased viscosity (polycythemia) have been reported in association with episodic vertebral-basilar insufficiency. Other causes of relative hypoxia, such as pulmonary disease, or disturbed brain cell metabolism (as in hypoglycemia) may also precipitate identical symptoms.

The mechanism of production of symptoms in the so-called "subclavian steal syndrome" may conveniently be discussed at this point. This subject was thoroughly reviewed by Patel and Toole in 1965.[6] In general, it has been demonstrated that arterial obstruction in strategic locations may cause reversal of normal arterial pressure gradients and actually cause blood to flow in a reverse direction. When the subclavian artery proximal to the origin of the vertebral artery is markedly narrowed or occluded, blood flow in the ipsilateral vertebral artery may actually be in a reverse direction and be a major source of blood to the arm via the distal subclavian and brachial arteries. The arm may thus be supplied with blood at the expense of the vertebral-basilar system, giving rise to symptoms of vertebral-basilar insufficiency.

While atherosclerosis of the proximal subclavian artery has been found to be the most common cause of the "subclavian steal" syndrome, other rare causes have been noted, such as coarctation of the aorta, congenital subclavian atresia, giant cell arteritis, trauma with subintimal dissection of the subclavian artery, and an aftermath of the Blalock-Taussig procedure.

Cardiac Abnormalities

Ischemic or valvular heart disease may be a major cause of cerebral ischemic symptoms due to intermittent and transient drops in cardiac output, related to either myocardial

TABLE 2

Symptoms And Signs of Vertebral-Basilar Disease

Structure And Arterial Supply	Symptoms And Signs
A. *Medulla and Upper Cervical Spinal Cord.* [anterior spinal artery, posterior inferior cerebellar arteries, small vertebral artery branches.]	Dysarthria and dysphagia Weakness or paresis all 4 limbs Drop attacks Hypalgesia—unilateral or bilateral Vertigo, nausea and vomiting Ataxia Horner's syndrome Facial dysesthesias
B. *Cerebellum.* [posterior and anterior inferior cerebellar and superior cerebellar arteries.]	Ataxia Dysmetria Dyssynergia
C. *Labyrinth and Cochlea* (?) [internal auditory artery.]	Vertigo, nausea and vomiting Tinnitus Acute onset deafness
D. *Pons and Midbrain.* [basilar and proximal posterior cerebral arteries]	Light headedness and/or syncope Confusion, stupor or coma Diplopia and ocular palsies Hypalgesia and weakness—unilateral or bilateral Paroxysmal hypertension Headache, suboccipital
E. *Thalamus and Subthalamus* [posterior cerebral artery.]	Thalamic syndrome Anesthesia dolorosa Tremor Hemiballism
F. *Cerebral Hemispheres — Occipital and Temporoparietal.* [posterior cerebral artery.]	Visual field defects Teichopsias and visual hallucinations Cortical blindness Focal cerebral deficits, [aphasia, dyslexia, visual agnosia, etc.] Temporal lobe seizures

ischemia or arrhythmias.

Clinical Manifestations

The symptoms and signs in vertebral-basilar insufficiency[7,8,9] may be easily and closely correlated with the function of those neural structures rendered temporarily ischemic (Table 2).

The *frequency* with which these episodes of insufficiency occur in the individual patient may vary greatly. The *duration* of this episodic neurological dysfunction is usually measured in minutes. It may persist for several hours but, by definition, must be of less than 24 hours' duration.

The most frequent symptom complex encountered is probably that of *vertigo* (with or without a sense of faintness), often with some *visual disorder* (visual field defect, hallucination or diplopia) and some evidence of localized *brain stem dysfunction* (dysarthria, dysphagia, facial dysesthesia, etc.).

Vertigo

This symptom is present in two thirds of the patients and may vary in intensity from minimal disability to severe prostration. It is usually not accompanied by tinnitus and hearing loss. It is often aggravated by movement of the head, eyes, or neck, or by body position changes.

Visual Disorders

As an isolated symptom, "spots in front of the eyes" may be the most common but is frequently ignored by the patient. Teichopsias of various types (black or white spots, "floaters", wavy lines) are described by about one half of patients. More complexly formed hallucinations such as zig-zag lines, coloured lights and patterns, and even formed coloured objects may occur. Visual field defects are less common and consist of homonymous or bilateral hemianopsias or quadrantanopsias. Visual illusions and distortions (e.g., "seeing through water") also occur.

Visceral Sensations

Nausea and vomiting are common. Patients may have flushing and sweating and experience choking thoracic sensations or feelings of impending doom. Some of these symptoms may resemble temporal lobe or diencephalic seizures.

Drop Attacks

Sudden unpredictable falling to the ground without loss of consciousness occurs in about 15 per cent of patients and is virtually pathognomonic of vertebral-basilar insufficiency.

Headache

Headache is a prominent symptom in about 10 per cent of patients. The pain is often intense, is usually located in the occipital or suboccipital area, and is generally throbbing in quality and aggravated by change in position. It may be accompanied by neck stiffness and occipital tenderness. Occasionally the headache may be unilateral in any part of the head, and the combination of severe headache with visual disturbance and severe nausea may resemble migraine.

Disturbance of Consciousness

Disturbance of consciousness occurs at some time in about one third of patients but is usually mild and transient, such as a brief clouding of consciousness. Syncope may occur due to brain-stem ischemia and occasionally may be followed by a seizure. Loss of consciousness without any other symptom or sign does not occur in vertebral-basilar insufficiency.

Hemiparesis

Hemiparetic symptoms are uncommon and when present are usually transient and minor. If recurrent, the paresis often fluctuates from side to side or involves both sides simultaneously. Occasionally, a quadriparesis with pseudobulbar symptoms may occur. *Sensory symptoms,* especially dysesthesias around the mouth, scalp, and neck, are common.

Differential Diagnosis

In the evaluation of symptoms and signs of vertebral-basilar insufficiency it is important that the diagnosis of *"subclavian steal"* be considered and looked for specifically. These patients may complain of symptoms of vertebral-basilar insufficiency precipitated by exercise of the arm on the same side (and occasionally of the contralateral arm). They may also complain of arm symptoms such as claudication, tingling, or numbness on exercise of the limb.

Significant *signs* of the "subclavian steal" syndrome are:

1. A decrease in radial pulse and in systolic

blood pressure of more than 20 mm. mercury on the affected side. This disparity in pulse and blood pressure may be more marked when erect or after exercise of the arm.

2. A delay in the time of appearance of the radial pulse on the affected side is pathognomonic of the syndrome.
3. A bruit may be audible over the vertebral or subclavian arteries, usually on the same side.

This syndrome should be recognized; as it represents a potentially treatable cause of vertebral-basilar insufficiency. However, it must also be stated that the natural history of these lesions is not yet known and spontaneous remissions of symptoms may occur.

Many other disease processes, as listed in Table 3, may mimic the symptoms and signs of vertebral-basilar insufficiency. Of these, Meniere's syndrome may be one of the most difficult to differentiate. It is, however, usually of much longer duration and often accompanied by tinnitus and hearing loss.

Angiography

Angiographic visualization of the vertebral and basilar arteries in the presence of significant atherosclerotic disease in these vessels may occasionally cause infarction of the central nervous system tissues supplied by these arteries. Angiography should, therefore, be undertaken only when:

(a) an intracranial surgically-correctable lesion must be ruled out,
(b) a correctable vascular lesion is probably present, (e.g., "subclavian steal"), or
(c) incapacitating insufficiency is present which does not respond to medical management.

Treatment

The primary aim of treatment is to prevent further episodes of vertebral-basilar insufficiency and, hopefully, to prevent the development of infarction of tissue in the same arterial distribution.

Meticulous attention should be paid to all possible etiological factors and other possible diagnoses, as listed in Tables 1 and 3.

Blood Pressure

The blood pressure should be watched carefully and the effects of rapid postural changes on blood pressure should be noted. Always check the blood pressure in both arms. If the blood pressure appears excessively high, that is, with diastolic pressures greater than 110-120 mm. mercury, attempts should be made at gradual lowering of the blood pressure. It should be noted, however, that some patients first develop symptoms of insufficiency after even modest antihypertensive therapy. It is possible that some patients with vertebral-basilar insufficiency need a slightly elevated blood pressure for adequate perfusion to occur. Therefore, moderate hypertension should not be vigorously treated in the face of this clinical picture. However, if there is any suggestion of even moderate postural hypotension as indicated by symptoms or actual blood pressure measurements, a trial of elastic leg bandages or stockings and even an abdominal binder or girdle should be instituted.

Severe *anemia* should be corrected if present. *Polycythemia* may also give rise to transient symptoms.

Anticoagulants

Anticoagulation therapy probably represents the treatment of choice if other general medical measures do not result in cessation of these episodes. It should be stated, however, that the final answer regarding the efficacy of anticoagulant therapy in the treatment of cerebrovascular disorders, including vertebral-basilar insufficiency, is not yet available. At the present time, it would appear that the best response to anticoagulant therapy in the treatment of cerebrovascular disease is seen in patients with

TABLE 3
Differential Diagnosis Of Vertebral-Basilar Insufficiency

Carotid insufficiency
Meniere's syndrome
Acute labyrinthitis
Cerebellopontine angle tumor
Cerebellar tumor—especially metastatic
Hypotensive episodes
Carotid sinus sensitivity
Hypoglycemic attacks
Drug intoxication—especially barbiturates
Migraine
Hyperventilation syndrome
Multiple sclerosis

insufficiency or progressive infarction in the vertebral-basilar system. Some reports have demonstrated a marked decrease in the incidence of subsequent ischemic episodes while on anticoagulants, while other studies have shown a very minor or no decrease in the frequency of episodes. Despite these inconsistencies, it is the consensus of many, but not all neurologists, that anticoagulation should be used, often as an emergency measure, in patients with insufficiency or progressive stroke in the vertebral-basilar system.

Patients that appear to respond best to anticoagulant therapy are those who have experienced many episodes within a relatively short period of time. It is possible that these patients represent embolization from thrombi in the proximal neck vessels.

The usual precautions regarding anticoagulant therapy will, of course, prevail. Lumbar puncture should be performed prior to institution of therapy to rule out intracranial and subarachnoid hemorrhage. Modest hypertension has not usually been considered a contraindication but may be treated concomitantly (but cautiously!). The coumarin compounds are used routinely, although in occasional cases where progressive infarction is apparent or seems imminent, heparin may be used to initiate therapy.

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IT'S THE LAW

No Liability for Hepatitis Following Transfusion

A hospital and surgeon won a verdict in a suit by an Illinois trial court. A patient, who developed serum hepatitis following transfusion of two pints of blood during the course of an operation, was denied compensation. The infection was held to be a calculated risk of blood transfusion.

An expert witness for the surgeon and for the hospital testified that there is no known test whereby the presence of hepatitis virus can be detected. The director of the blood bank testified that the virus occurs in 0.3 per cent of blood donors, and that hepatitis is a calculated risk in blood transfusion.

Case Reference: Matter of Inter-Country Blood Banks, Inc. and Local 854, International Brotherhood of Teamsters, 31 SLRB No. 12 (N.Y., Feb. 21, 1968)
The Citation—17: 2, May 1, 1968.

Spectrocromists

This was an establishment operated through advising individuals to wear clothing according to the color of the spectrum. How they came to the conclusion as to what part of the spectrum the individual should assume, in selecting his colors, is not clear. Perhaps it was for this advice they charged. They have been arrested and fined.*

*Morris Fishbein, M.D.: The New Medical Follies, 1927.

Nobel Prize Winners in Medicine and Physiology

Ronald Ross 1902

For his work on malaria, by which he has shown how it enters the organism and thereby has laid the foundation for successful research on this disease and how to combat it.

"Towards the middle of August (1897) I had exhaustively searched numerous grey mosquitoes and a few brindled mosquitoes. The results were absolutely negative; the insects contained nothing whatever.

"I had remembered the small dapple-winged mosquitoes (genus Anopheles), but as I could not succeed either in finding their larvae or in inducing the adult insects to bite patients, I could make no experiments with them. On the 15th of August, however, one of my assistants brought me a bottle of larvae, many of which hatched out next day. Among them I found several dapple-winged mosquitoes, evidently of the same genus as those found about the barracks, but much larger and stronger. Delighted with this capture I fed them on a case with crescents in the blood."

After unsuccessful dissection and examination of six of these insects Ross had only two left.

"The seventh dapple-winged mosquito was then successfully dissected. Every cell was searched, and to my intense disappointment nothing whatever was found, until I came to the insect's stomach. There, however, just as I was about to abandon the examination, I saw a very delicate circular cell apparently lying among the ordinary cells of the organ, and scarcely distinguishable from them. Almost instinctively I felt that here was something new. On looking further, another and another similar object presented itself. I now focussed the lens carefully on one of these, and found that it contained a few minute granules of some black substance exactly like the pigment of the parasite of malaria . . . After mounting the preparation I went home and slept for nearly an hour. On waking, my first thought was that the problem was solved; and so it was.

"The next morning the eighth and last dapple-winged mosquito was killed and dissected with much anxiety. *Similar bodies were present in it.* The objects lay, not in the stomach cavity of the insects, but in the thickness of the stomach wall.

"These two observations solved the malaria problem . . . At a stroke they gave both of the unknown quantities—the kind of mosquito implicated and the position and appearance of the parasites within it."*

*With acknowledgments to Theodore Sourkes: Nobel Prize Winners in Medicine and Physiology, 1966.

Oof Da!

Medicine must have been much simpler in the time of John of Mirfield, when, according to him, successful physicians required only three special qualities: "to be able to lie in a subtle manner, to show an outward honesty, and to kill with audacity."*

*Harvey Graham: A Doctor's London.

Brain Abscess *

ZONDAL MILLER, M.D.
St. Paul, Minnesota

SUPPURATION IN THE intracranial cavity results in meningitic, encephalitic reactions and brain abscess formation. When a neurologist or neurosurgeon first sees the patient, rarely is it evident that a brain abscess exists unless it is known the patient has previously been diagnosed as having a purulent sinusitis, otitis media, mastoiditis, or a penetrating head injury. A diagnosis of a brain abscess caused by other than direct extension is most difficult to make, especially in our present antibiotic era, as there has been a decrease in the direct extension pathogenic cases and an increase in the metastatic forms. With the advent of effective antibacterial chemotherapy, the treatment of intracranial suppurative disease has been profoundly altered. Some of these diseases, for example, intracranial thrombophlebitis, bacterial meningitis, and certain cases of extradural abscess, can be managed entirely by the use of antibiotic medication. In others, such as subdural empyema and brain abscess, the use of antibiotics has greatly facilitated the treatment, even though the ultimate therapy is surgical.

In the pre-antibiotic era the mortality was approximately 50%. Prior to World War II, the mortality rate at Massachusetts General Hospital was approximately 80%, and from a period of 1946 to 1950 it was 34%. Other large groups have reported mortality figures of 45-80% prior to antibiotics, and a reduction to 30-40% in our present chemotherapeutic era. Problems in recognition and management of brain abscesses still remain a formidable problem. Furthermore, the patient who survives the surgical removal of a brain abscess may still be left with permanent neurologic disabilities.

Surgical intervention began with Macewen in 1880. The three major objectives in the treatment of a brain abscess are: (1) to save the patient's life, (2) to preserve or restore optimum neurologic function, (3) to prevent

*Presented at the Continuation Course in Neurological Emergencies sponsored by the University of Minnesota, Minneapolis, November 8, 1967.

disabling sequelae such as epilepsy, aphasia, and hemiplegia.

Pathogenesis

With the exception of a relatively small number of cases (other than the large number occurring during armed conflict) in which infection may be introduced from the outside, for example, via penetrating missiles, compound fractures of the skull, and intracranial operations, the occurrence of a brain abscess is almost always secondary to a focus of suppuration elsewhere in the body.

Chronic Otitis Media

Prior to antibiotics, chronic otitis media accounted for somewhat more than half of all the cases of intracranial abscess formation. Even now it still may represent the most important cause. In these cases the abscess is most frequently found in the temporal lobe and next in the cerebellum; rarely does it occur in other parts of the brain or in multiple formation. The method of spreading is usually by direct extension, in which the roof of the tympanic cavity or mastoid bone becomes the nidus of osteomyelitis with secondary necrosis and perforation. The overlying dura becomes inflamed, with spread by way of the perivascular spaces. Thrombophlebitis of the pial veins and dural sinuses provides the mechanism for the formation of brain abscesses by blocking normal blood flow and causing infarction of brain tissue, which then renders this area more vulnerable to the infectious material. Experimental data in animals indicate that infarction of tissue is the most important factor in the development of brain abscess. The spread along venous channels also explains how a cerebellar abscess can develop from the contiguous phlebitis of the lateral sinus, and also how frontal lobe or parietal lobe abscesses may develop from the distant source of infection in the middle ear.

Infection of Nasal Cavity and Sinuses

Infections of the nasal cavity and accessory sinuses also constitute an important source for intracranial abscess formation; it has been estimated that approximately 20% of such abscesses have their origin from infected sinuses. The most frequently involved sinuses are the frontal, ethmoid, and sphenoidal. The inflammatory reaction tends to extend along the veins draining into the cavernous sinus with or without antecedent osteomyelitis.

Metastatic Infection

Over one third of brain abscesses are metastatic in origin, the most important sources being the lungs or pleurae (*thoracogenic*), and the heart (*cardiogenic*), and especially secondary to cases of congenital heart disease. However, on occasion, inflammation of the pelvic organs, abscessed teeth or tonsils, and osteomyelitis of non-cranial bones may metastasize to the cerebral hemispheres. Bronchiectasis is also a frequent source. Usually abscesses secondary to pleuropulmonary disease are multiple in over 40% of cases; the metastatic formation tends to affect the frontal, parietal, and occipital parts of the brain with about equal frequency, rarely involving the temporal regions or cerebellum. The heart is an important source of metastatic brain abscess formation due to either fragments of infected vegetation from the heart valves or because of congenital defects permitting shortcircuiting of the pulmonary circulation, thus allowing infected emboli to reach the vessels of the brain, causing infarction of the brain tissue with only a restricted inflammatory response about the involved vessel. Spinal fluid in these cases seldom shows more than a slight increase in the polymorphonuclears and, occasionally, some red blood cells.

It has been postulated that the chronicity of the viridans infection allows the central nervous system tissue to develop an immunity to the organism. However, an acute bacterial ulcerative endocarditis, the type frequently caused by staphylococcus, hemolytic streptococcus, or pneumococcus bacteria, which usually runs a fulminating course, frequently gives rise to multiple small abscesses of the brain, as it does to many other organs of the body. Approximately 5-10% of cases of *congenital heart disease* result in brain abscess, usually solitary, and rarely seen before the third decade.

Unidentified Cause

It should be emphasized that in a small portion, somewhere between 5-15%, a primary focus of infection cannot be found and may not be discovered even at autopsy. In a num-

ber of cases the primary source of infection appears only after a brain abscess has been recognized and successfully treated.

The organisms responsible for brain abscesses are remarkably diverse. An abscess may contain only a single organism; but more frequently several organisms are present. Those deriving from the middle ear or paranasal sinuses are the staphylococcus, streptococcus, and pneumococcus, but various anaerobic strains of streptococci, diphtheroid, and fusiform bacilli may also be present.

Metastatic abscesses are caused by an even greater variety of pathogens. Anaerobic streptococci are commonly found in abscesses secondary to congenital heart disease. Unusual abscesses may be due to typhoid bacillus, clostridium, and various fungal organisms such as actinomyces. In a number of cases the pus from an abscess will be sterile. Blood cultures show growth only in those cases associated with septicemia. As a rule, spinal fluid culture discloses no growth unless the abscess is associated with purulent meningitis, resulting from a rupture of the abscess. In those cases where more than one organism is found on culture of the spinal fluid, the physician should be alerted to the diagnosis of a brain abscess. The abscesses, as a rule, develop in the white matter, which has a poor blood supply in contrast to the cortex; and most of them originate just subcortically as an area of cerebritis with a necrotizing center that has a poorly defined inflammatory zone. Subsequently a variable capsule formation develops. When formed the capsule may be incomplete and the abscess may thereafter be unilocular or multilocular. It may continue to enlarge by thrombosis of the adjacent vessels and by secondary necrosis, usually in a direction toward the centrum, making it much more likely to rupture into the ventricles than into the subarachnoid space.

Diagnostic Consideration

The diagnosis of a brain abscess remains difficult and treacherous. Simple awareness that it may exist is of prime importance.

Headache

The initial symptom of intracranial infection is headache, the one symptom almost invariably present. The appearance of a headache or any neurologic symptom which cannot be explained by the known primary infection should always alert the doctor to the danger of an abscess formation; and he should be especially concerned regarding the development of an acute headache in individuals known to have congenital heart disease. Other presenting symptoms include profound lethargy, mental confusion, hyperirritability, stupor, nausea, emesis, and focal or generalized seizures. In most cases the headache is more severe on one side and tends to increase in severity as the disease progresses, though it may decrease as encapsulation occurs.

Neurologic Signs

Localizing neurologic signs appear sooner or later in almost all cases; but, like papilledema, they appear relatively late in the course of the illness, when it may be too late for instituting a successful therapeutic regime. Of course the nature of focal signs will depend upon the locality of the abscess. Whereas headache may be the most prominent feature in most patients, focal seizures may predominate in others, and still another group may present only with signs of increased intracranial pressure. The development of new neurologic signs is usually rapid. In a few cases the evolution is slower; and in those with an indolent course a mistaken diagnosis of a cerebral neoplasm is frequently made.

The more acute symptoms and signs are usually associated with the encephalitic reaction prior to encapsulation. With the latter, the patient tends to improve and the physician may be "red-dogged" into complacency. Subsequently, worsening may result from abscess rupture or the development of increased intracranial pressure and subsequent medial temporal lobe or cerebellar tonsil herniation.

Other Signs and Symptoms

Seizures occur in about the same frequency noted in large series of cerebral neoplasms, about 25-30%. Frequently the patient presents with predominant signs of *meningeal reaction,* and the half-diagnosis of meningitis or encephalitis is made. If focal signs occur with the meningo-encephalitic reaction, the diagnosis of brain abscess becomes easier. The patient with a brain abscess may show a *moderate temperature elevation* between 100-102° and a mild polymorphonuclear leukocytosis.

However, on occasion, particularly in those with chronic and encapsulated abscesses, there may be no fever, or the temperature may actually be below normal. In the average case, the cerebrospinal fluid pressure is moderately increased but is apt to be quite high in the more advanced cases. In the absence of generalized meningitis, the cell count may range from five to 300 cells, occasionally higher with the more acute cases having a predominance of neutrophils. In rare cases there may be only a few lymphocytes and in some cases no pleocytosis. The *spinal fluid protein* is almost invariably elevated, and spinal fluid sugar is not below normal unless there is an associated meningitis.

Diagnostic studies which are helpful include x-rays of the chest, skull, sinuses, and mastoids, readily available at any hospital. An electroencephalogram may be quite informative, especially for finding a delta focus in the presence of a meningo-encephalitic reaction. Other specialized procedures include brain scanning, angiograms, and air studies. Kahn, in 1939, recommended the injection of 2-3 cc. of thorotrast in the abscess cavity at the time of the initial aspiration. This material is taken up by phagocytes in the wall of the abscess so that subsequent x-ray study will reveal the size of the lesion and determine whether therapy has been effective.

Differential Diagnosis

A differential diagnosis of a brain abscess must include epidural abscess, subdural abscess, cerebral thrombophlebitis, focal embolic infarction, acute necrotizing hemorrhagic encephalopathy, primary and metastatic neoplasms, especially metastatic meningeal carcinomatosis and, occasionally, massive ischemic infarction. Extradural abscesses rarely reach sufficient proportion to cause increased intracranial pressure. Irregular fever, local headache, tenderness over the affected region, and a mild pleocytosis of the spinal fluid are its main manifestations.

Subdural empyema is a highly lethal complication of frontal osteomyelitis and sinusitis and is rarely secondary to chronic otitis media. As subdural pus accumulates over the frontal lobe, there is apt to be rapid progression of mental obtundency, stiff neck, stupor, and hemiplegia, with or without focal generalized seizures.

Intracranial thrombophlebitis is a frequent complication of suppurative meningitis, usually manifesting itself four to 10 days after the onset of meningitis by a burst of seizures, focal neurologic signs, and exacerbation of fever. The lateral, cavernous, and superior longitudinal sinuses are frequently affected by a spread of infection from the middle ear, skin of the face, or frontal sinus. All of these varieties are characterized by a high remittent fever.

Management of Brain Abscesses

The presence or absence of a brain abscess is ultimately determined by exploring the brain with a ventricular needle through a burr hold or craniotomy. This procedure not only confirms the diagnosis but constitutes the first step in treatment. The abscess is drained, and contrast material, along with a mixture of the broad-spectrum antibiotics, is frequently injected into the abscess cavity. Cultures of the pus are made to determine the appropriate antibiotic therapy, to be given orally or parenterally. Subsequent skull films are taken to determine the size and position of the lesion. The neurosurgeon may prefer to aspirate the septic focus repeatedly; others may totally excise the septic area after initial aspiration.

Repeated aspiration is the treatment of choice if the abscess is deeply located, poorly encapsulated, or situated in a strategic motor or speech area. Most surgeons, however, are reluctant to depend upon the effects of aspiration alone, since many abscesses may have multiple non-communicating loculi, only one of which is being tapped and visualized by the contrast material. In fact, while one abscess cavity is healing, another may be ripening for rupture. If the patient's condition permits, total excision of a well-encapsulated abscess is far less damaging to brain tissue than wide excision of a poorly demarcated area of suppuration. Metastatic abscesses are more progressive and malignant and less apt to form capsules due to the virulence of the organism and insufficient host resistance. The surgical treatment of such an abscess is a difficult and complex problem, and one that cannot be standardized for every patient. The most impor-

tant key to success is early recognition that an abscess exists.

Case Report

Case 1

A 33-year-old male was admitted to St. John's Hospital, March 4, 1961, with a history of flu-like symptoms and a mild fever for a week prior to admission. His wife was also treated for a flu syndrome. On the day of admission, the patient was drowsy, with a mild temperature of 99.4°, which subsequently became normal. He had a bradycardia, with a pulse ranging from 42-48. There was some questionable exposure to lead paint. He was first seen in consultation March 8 and was lethargic, though he could be aroused, whereupon he became hyperirritable. He did not communicate. Neurologic examination, in addition, revealed his pupils to be 3 mm. in diameter and equal. No papilledema was noted; eye signs were normal. There was mild neck rigidity and mild reflex changes with an increase in the left knee jerk and a decrease in the left cremasteric reflex along with a positive left Babinski. Laboratory studies performed prior to consultation disclosed a hemoglobin of 14.1 gm., a WBC of 9,000 with 68% polys, and a sedimentation rate of 62. Spinal fluid showed elevation of the cerebrospinal fluid pressure with a reading of over 500 mm. in the upright position. Spinal fluid analysis revealed 45 white cells with 97% lymphocytes, a protein of 101 mg. and a sugar of 33 mg. The working diagnosis was that of encephalitis. However, because of increasing stupor and the development of disconjugate eye movements, further studies were performed. Prior chest and skull x-rays had been normal. An angiogram on March 11, 1961, disclosed a large lesion in the left frontal area. At craniotomy, green pus with a fecal odor was encountered, and approximately two ounces of pus was drained. Subsequently, complete extirpation of the abscess and the capsule was accomplished. Postoperatively the patient was decerebrate, with a progressive downhill course and expiration March 29, 1961, 18 days after surgery. Culture of the purulent material revealed anaerobic streptococcus. Autopsy was not granted.

Comment: An original diagnosis of encephalitis became less evident as the patient showed increasing neurologic signs and symptoms, and as angiography disclosed, the mass lesion and abscess formation was found at craniotomy. This is a case of presumed metastatic source; however, the primary focus was not determined.

Case 2

A four-year-old child was admitted to St. John's Hospital, November 10, 1964. He had previously been treated for an upper respiratory infection but was not responding to antibiotic therapy, which included gantrisin orally. At the time of admission the patient was dehydrated and was vomiting. His temperature was 99.8° and shortly thereafter dropped to 97°. Later he was lethargic and difficult to arouse, and it was noted that he had a mild neck rigidity. His chest was clear, there were no heart murmurs, and ear- nose- and throat-examination was negative. Spinal tap five hours after admission disclosed clear, colorless fluids with 52 white cells, predominantly mononuclears, with a sugar of 62 mg. %, and a protein of 57 mg. %. Hemoglobin was 10 gm., WBC 10,500, with 84% neutrophils.

Shortly after spinal puncture the child developed flaccid paralysis and became comatose, with episodes of opisthotonus positive Babinskis, and then respiratory paralysis. He was maintained on a Bennett respirator for 12 hours, until expiration. Prior to death, the child had been seen by a neurosurgeon, who found no papilledema, equal pupils, and mild neck rigidity. The eyes were slightly deviated to the left, and there was unsustained bilateral clonus with a positive right Babinski. At autopsy an abscess was found in the right lobe of the cerebellum, coning of the cerebellar tonsils, and slight coning of the medial temporal lobes. Culture of the pus disclosed beta hemolytic streptococcus. The primary source was not discovered.

Comment: Another case of metastatic brain abscess with unknown primary source and a rapid downhill course best explained by herniation of the cerebellar tonsils following spinal fluid puncture.

Case 3

A child was admitted to St. John's Hospital, January 12, 1961, with a four-day history of nausea, vomiting, headaches, and lethargy. Admission diagnosis was that of gastroenteritis. The patient was afebrile with a white count of 8,500, 65% polymorphonuclears and 34% lymphocytes. Hemoglobin was 12.3; chemistry was negative, except for 2+ cephalin flocculation at 24 hours, and 4+ at 48 hours. The child was seen by a pediatrician January 17, 1961, with a tentative diagnosis of electrolyte imbalance and hepatitis. The temperature and white count remained normal. Spinal fluid examination performed January 17 disclosed one white cell protein of 77 mg. %, a sugar of 78 mg. %, and chlorides of 123. The patient was first seen in neurologic consultation on January 21, 1961; the examination disclosed a lethargic child who could be aroused, with ensuing hyperirritability. Pupils were active and equal, and ocular movements normal. There was crack-pot resonance on percussion of the skull, along with papilledema of the right eye. Mild neck rigidity was present.

Approximately 12 hours after neurologic consultation January 21, 1961, the child developed repeated focal seizures, involving the left arm and then the entire left side, and subsequently the seizures became generalized. Previous x-rays had disclosed a normal chest January 17, a small bowel ileus, and a normal skull on January 21. A right cerebral angiogram, performed shortly after the child went into repeated seizures, disclosed a marked shift of the anterior cerebral vessels across the midline to the left, indicating a large right frontal mass. A ventriculogram was also performed, disclosing a marked shift to the left, including the third ventricle. There was incomplete filling of the right frontal horn. Immediate craniotomy was performed after the child had become comatose, with widely dilated pupils, following the ventriculogram. Craniotomy encountered a large pus pocket; and the abscess, which was encapsulated, was excised. The child, however, never regained consciousness, remained decerebrate, and expired less than 12 hours after the diagnosis of a brain abscess had been established. Culture revealed nonhemolytic streptococcus. Autopsy was not granted.

Comment: The child was originally diagnosed as having

gastroenteritis with subsequent change of diagnosis to probable hepatitis; when he developed lethargy and papilledema, a diagnosis of a cerebral neoplasm was entertained. However, a craniotomy disclosed a large right frontal brain abscess. Unfortunately treatment was begun too late to be effective.

Case 4

A 33-year-old patient was first seen in neurologic consultation December 7, 1959, complaining of gait disturbance with a known history of onset of weakness in the left leg at age 29. Neurologic examination disclosed hyperreflexia with clonus of the left leg and positive toe signs on the left, as well as decreased superficial reflexes over the left abdomen and a mild increase in reflexes of the left arm. Cranial nerve examination and a Schillings test were negative. Hemoglobin was 13.7, with normal WBC. Spinal fluid protein was 44 mg. %; sugar was 70 mg. %; there were no cells and a normal gold curve. Spine x-rays and a complete myelogram, all the way to the foramen magnum, were negative. A diagnosis of a spinal form of multiple sclerosis was made.

The patient was admitted to St. John's Hospital February 17, 1961, after an episode of acute onset of weakness of the right arm and right-sided Jacksonian seizures, confined to the right arm with later spread to the right side of the face. Severe headaches without emesis were present. On admission his temperature was 99.2°, and on the following day, 101.4°; otherwise it was normal. On February 23, 1961, the patient progressed to a complete right hemiparesis. No papilledema was present. On February 20, 1961, a left cerebral angiogram suggested depression in the callosal vessels. A pneumoencephalogram February 21, 1961, disclosed the left lateral ventricle to be depressed and displaced slightly toward the right. Previous skull and chest x-rays were negative. Spinal fluid protein revealed 75 mg. % and no pleocytosis. On February 23, 1961, a left craniotomy was performed, and an abscess cavity was encountered in the left superior parietal area. Approximately 15 cc. of pus were removed, and culture of this material revealed nonhemolytic streptococcus. Subsequently the abscess was repeatedly drained and the patient was placed on oral antibiotics, including chloromycetin and streptomycetin. Though he recovered from the operation, he was left with a mild to moderate expressive aphasia and subsequent focal Jacksonian and grand-mal seizures, which were eventually controlled by anti-convulsants.

Comment: This case demonstrates successful cure of a brain abscess in an individual previously diagnosed as also having multiple sclerosis.

Case 5

This patient, age 23, known to have a congenital cardiac defect and a Klippel-Feil deformity, was admitted to Miller Hospital, December 3, 1964, with a fever of 103°, headache, emesis, and a stiff neck. Nine days prior to admission she had complained of nausea, diarrhea, and one fainting spell. Three days later she improved only to regress with subsequent malaise and listlessness. A week prior to admission a temperature of 101° had been noted. The night prior to admission she had developed an acute headache with stiffness of the back and neck and excessive sweating. When seen in consultation six hours after admission, her temperature was 102°, pulse 108, respiration 60. Obvious Klippel-Feil deformity was noted with an extremely short neck. There were cardiac enlargement with systolic and diastolic murmurs, strongly positive meningeal signs, vertical nystagmus, constricted visual fields, and no papilledema. Spinal puncture in the decubital position disclosed an opening pressure of 560 mm. of water. The spinal fluid was thick and turbid, containing 635,000 cells per cc., predominantly polymorphonuclear leukocytes. Protein was 860 mg. %, and no sugar was present in the spinal fluid. Sedimentation rate was 1, hemoglobin 14.4, white count 23,100 with 94% polymorphonuclear neutrophil leukocytes, and a later white count to 36,300.

The patient was treated with massive intravenous injection of penicillin and chloromycetin. The next morning she was confused and lethargic and developed disconjugate eye movements. The right pupil later became fixed, and the patient became decerebrate shortly prior to expiration on December 4, 1964, 28 hours after she was admitted to the hospital. At autopsy a brain abscess 5 cm. in largest diameter was found in the right occipital area with rupture into the ventricles and a secondary basilar meningitis. Marantic vegetations were found in the mitral valve. There was a cor triloculare with a single ventricle, without any transposition of the vessels, and a Klippel-Feil deformity. A spinal fluid and blood culture subsequently disclosed gamma streptococcus.

Comment: Case of a congenital heart deformity with marantic vegetations with secondary gamma streptococcus septicemia and a ruptured occipital brain abscess and purulent bacterial meningitis with expiration 28 hours after admission to the hospital.

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*Richard Dunlop: Doctors of the American Frontier, 1965.



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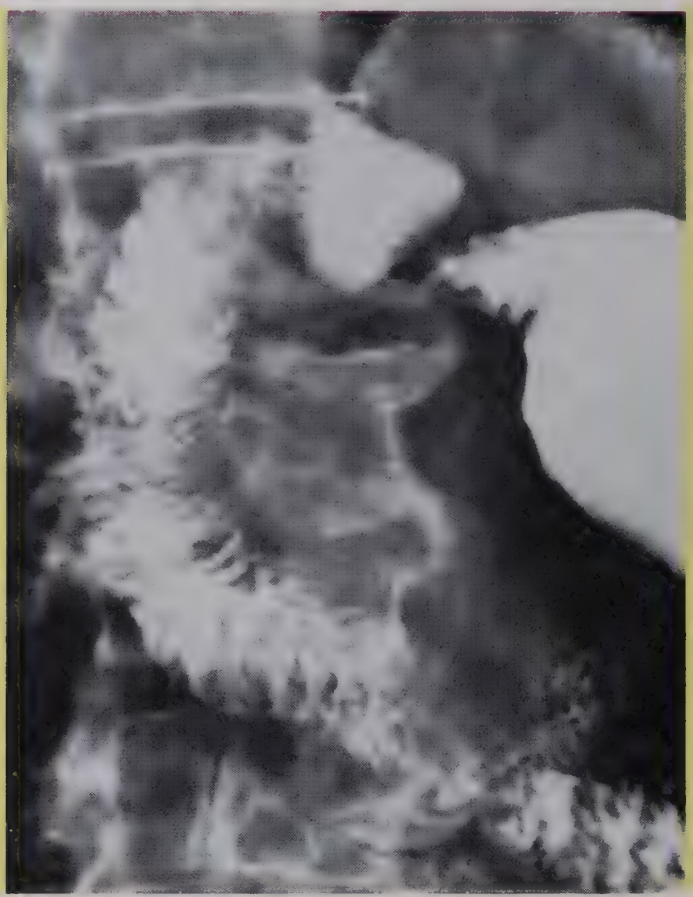
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In the hypotonic duodenograph[1,2] reproduced above, the gastrointestinal tract was relaxed with Pro-Banthine. The duodenum was intubated. Pro-Banthine in a dose of 60 mg. intramuscularly was used to assure prompt aperistalsis, and double-contrast visualization was achieved with ordinary barium and air.

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Contraindications: Glaucoma; severe cardiac disease.

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Dosage: The maximal tolerated dosage is usually the most effective. For most *adult* patients this will be four to six 15-mg. tablets daily in divided doses. In severe conditions as many as two tablets four to six times daily may be required. Pro-Banthine (brand of propantheline bromide) is supplied as tablets of 15 mg., as prolonged-acting tablets of 30 mg. and, for parenteral use, as serum-type vials of 30 mg. The parenteral dose should be adjusted to the patient's requirement and may be up to 30 mg. or more every six hours, intramuscularly or intravenously.

(1) Bilbao, M. K.; Frische, L. H.; Rösch, J., and Dotter, C. T.: Hypotonic Duodenography, Scientific Exhibit, Radiological Society of North America, Chicago, Nov. 27–Dec. 2, 1966.

(2) Bilbao, M. K.; Frische, L. H.; Dotter, C. T., and Rösch, J.: Hypotonic Duodenography, Radiology 89:438-443 (Sept.) 1967.

See also: Liotta, D.: Pour le diagnostic des tumeurs du pancréas: La duodénographie hypotonique, Lyon chir. 50:445-460 (May-June) 1955.

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Editorials

Case Finding in Cystic Fibrosis

In the January issue of Minnesota Medicine* is an article by Warwick and Koroshec describing mass screening techniques for cystic fibrosis and the results in Minnesota school children. These workers are to be commended on the prodigious effort expended in the testing of 20,071 children in 26 communities. The cooperation of the Mrs. Jaycees' organization and the school officials in this undertaking is an impressive example of the efforts of nonmedical personnel to work for the welfare of children.

Despite this great effort and the assistance of physicians in the community, no new cases were discovered in the tested group. However, three new cases were found among children who happened not to be in the tested group at the time.

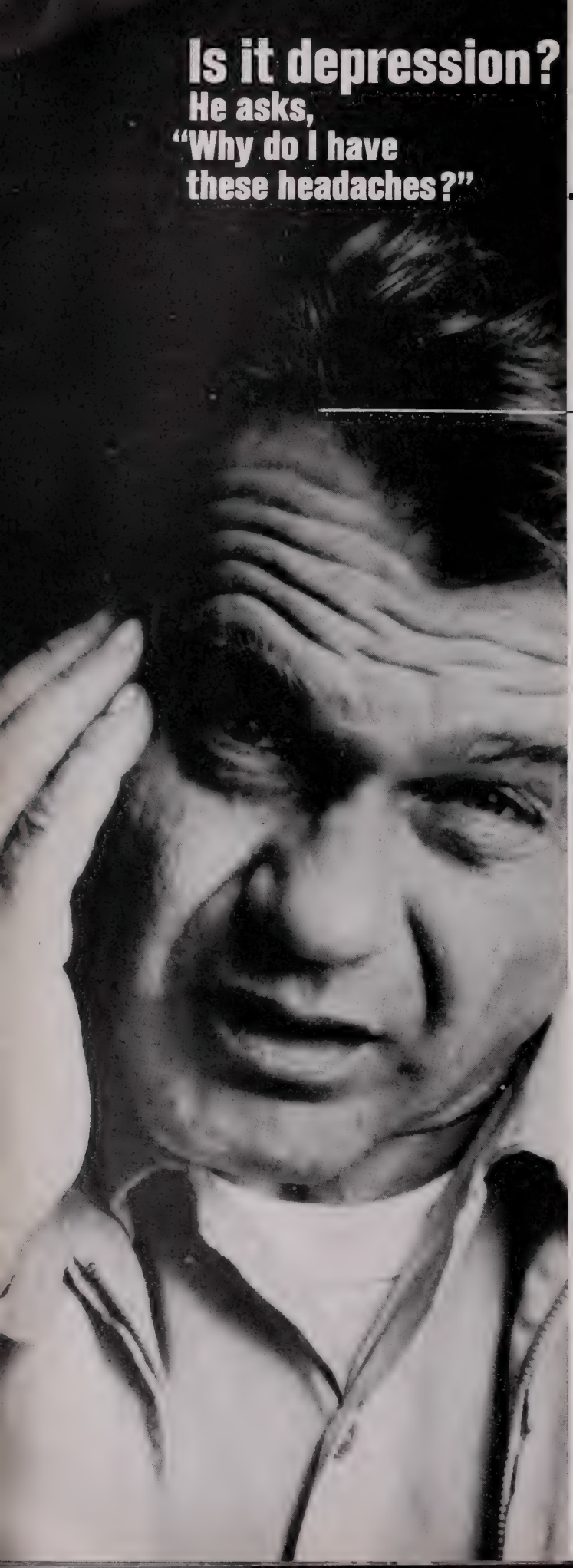
Dr. Warwick was able to support his view that the incidence of cystic fibrosis is one per 1,000 births.

Dr. Warwick makes a plea at the conclusion of his article for the consideration of newborn nursery screening for cystic fibrosis with his device for performing a heat stimulus-chloride ion electrode sweat test. This instrument in Dr. Warwick's hands has proved an accurate diagnostic aid in the laboratory, but several considerations are worthy of second thought. Among the 20,071 children were found 1,500 who had elevated values in the test. On subsequent retesting with iontophoresis techniques, these 1,500 children proved to be normal. This leaves one somewhat perplexed as to the accuracy of the instrument, or the efficiency of its use, or perhaps the range of values considered to be normal.

To the suggestion that mass screening in newborns be carried out for cystic fibrosis one may draw a parallel to the legislation now in effect demanding testing of newborn infants for phenylketonuria. Many pediatricians feel that this legislation was hastily enacted and ill-advised when the controversy still rages over the efficacy of dietary measures for children with elevated levels of serum phenylalanine, the rarity of the disease itself in the general population (one per 20,000 births), the finding of some normal individuals with elevated levels of serum phenylalanine who have not been treated, and lastly the expense involved in such mandatory testing with low yields.

Lest anyone immediately accept the conclusion that mass screening techniques for cystic fibrosis in infants is desirable, let alone worthy of legislation, what facts should be

*Warwick, W. J., and Koroshec, JoAnn: Cystic Fibrosis Detection Clinic Program in Minnesota. Minnesota Med. 51:153, 1968.



...but his other symptoms:
functional somatic complaints, anxiety, insomnia, loss of interes anorexia, feelings of guilt
strongly suggest an underlying depression.

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Precautions and Side Effects: Drowsiness may occur within first few days of therapy. Patients should be warned against d ing a car or operating machinery or appliances requiring al attention. When depression is accompanied by anxiety or ag tion too severe to be controlled by ELAVIL HCl alone, a phenoth zine tranquilizer may be given concomitantly. Suicide is alway possibility in mental depression and may remain until signific remission occurs. Supervise patients closely in case they n require hospitalization or concomitant electroshock thera Untoward reactions have been reported after the combined u of antidepressant agents having varying modes of activity. cordingly, consider possibility of potentiation in combined use antidepressants. Monoamine oxidase inhibitor drugs may pot tiate other drugs and such potentiation may even cause dea permit at least two weeks to elapse between administration of t agents; in such patients, initiate therapy with ELAVIL HCl c tiously with gradual increase in dosage required to obtain satisfactory response. Caution patients about errors of judgm due to change in mood, and that the response to alcohol m be potentiated. May provoke mania or hypomania in man depressive patients.

Side effects include drowsiness; dizziness; nausea; exciteme hypotension; fine tremor; jitteriness; weakness; headache; hea burn; anorexia; increased perspiration; incoordination; allerg type reactions manifested by skin rash, swelling of face a tongue, itching; numbness and tingling of limbs, including perip eral neuropathy; activation of schizophrenia which may requ phenothiazine tranquilizer therapy; epileptiform seizures chronic schizophrenics; temporary confusion, disturbed conce tration or, rarely, transient visual hallucinations on high dos evidence of anticholinergic activity, such as tachycardia, dryne of the mouth, blurring of vision, urinary retention, constipatic paralytic ileus; jaundice; agranulocytosis.

Careful observation of all patients is recommended. The an depressant activity may be evident within 3 or 4 days or may ta as long as 30 days to develop adequately, and lack of respon sometimes occurs. Response to medication will vary according severity as well as type of depression present. Elderly patier and adolescents can often be managed on lower dosage leve

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WHERE TODAY'S THEORY IS TOMORROW'S THERAP

considered? Cystic fibrosis is a serious but treatable disease. It occurs in varying degrees, the most serious variety causing death in early infancy. Dr. Warwick cites a figure of 36% as representing the mortality rate in cystic fibrotics during the first year of life. The least serious variety of cystic fibrosis causes varying degrees of disability from pulmonary disease in adults. One raises the question then: Is the disease diagnosable in the newborn without such obvious signs as meconium ileus? Since the disease is so serious in the tiny infant, how amenable to treatment is it? While answers to these questions are being pondered, perhaps it would be advisable to consider the present status of therapy in older children and adults.

Shwachman and associates[1] reported a series of 65 patients with cystic fibrosis who were over 17 years of age (mean 20½ years). Fifty-five were in what they termed "excellent" to "mild" clinical status, the other 10 being in "moderate" health. Follow-up care was good in most. In 34 the diagnosis was made before the age of 10 years. The authors state that the major factor in the maintenance of a good clinical state was the use of tetracycline in the treatment of pulmonary disease to keep the bronchopulmonary tree "clean." Additional credit must be afforded dietary therapy and pancreatic enzyme replacement.

Doershuk and co-workers[2] have evaluated the use of a comprehensive therapeutic program of hospital and home care with mist tent treatment, intermittent aerosol therapy, and segmental postural drainage plus antibiotic treatment. This regimen they judge to be effective in the arrest of the usual progression of pulmonary disease in cystic fibrosis. It would appear that the next step would be an evaluation of a prophylactic program on a random selection basis to determine whether the therapeutic program in patients with no pulmonary involvement would effectively prevent or offset the progressive pulmonary disease. However, the danger of promoting unjustifiable invalidism in children with diagnosed cystic fibrosis but without pulmonary disease would be a most cogent consideration.

Thus one concludes that both early diagnosis and careful and thorough medical follow-up materially affect morbidity and the prognosis for longevity in cystic fibrosis. But can this be further improved by infant screening techniques? Some doubt exists that the newborn can prove to be a satisfactory subject for screening tests in the light of providing adequate sweat samples. Additional considerations are the cost of the equipment and the training of nursery personnel in its proper use, particularly when the yield is apt to be so low.

It would seem more rational that the general practitioner and the pediatrician be continually alerted to the possibility of cystic fibrosis in any child who fails to thrive or who manifests pulmonary symptoms either of persistent or recurrent nature. It has been the policy of my colleagues and myself to carry out sweat tests on any child with symptoms of an asthmatic nature. We would agree that the younger the child the more pernicious the character of cystic fibrosis is likely to be and, consequently, the less amenable it is to therapy.

With the aforementioned reservations in mind we nevertheless await the efforts and the results of a pilot study by Dr. Warwick and co-workers in carrying out such testing in a large series of newborn infants. Those caring for children might be less in doubt regarding the wisdom of such a program if these workers can provide documentation for their thesis that mass screening for cystic fibrosis in newborns is practicable, accurate, and beneficial in reducing mortality from the disease.

Edmund C. Burke, M.D.
Rochester, Minnesota

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1. Shwachman, H., Kulczycki, L. L., and Khaw, K.-T.: Studies in Cystic Fibrosis: A Report on Sixty-five Patients Over 17 Years of Age. Pediatrics 36:689, 1965.

2. Doershuk, C. F., Matthews, L. W., Tucker, A. S., and Spector, S.: Evaluation of a Prophylactic and Therapeutic Program for Patients with Cystic Fibrosis. Pediatrics 36:675, 1965.

Among all human constructions the only ones that avoid the dissolving hands of time are castles in the air.—De Roberto



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Early Invasive Carcinoma of the Cervix*

A LARGE PART of the recognition of early cervical cancer has been the result of the ever wider application of the vaginal smear. This has raised some problems; but an infinitely greater good has resulted. For the first time there is a vision of the possibility of practically excluding deaths from a major cancer.

Some of the problems of the smear itself, its interpretation and handling, were discussed before this society last year. This discussion included the indications and techniques for the application of conization of the cervix. In this procedure the potentially cancerous surface of the endocervix and of at least a further centimeter in all directions of the surface of the vaginal portion of the cervix is removed for microscopic examination. A detailed diagnosis and the type of treatment to be applied should come from careful evaluation of this. Such conization is indicated only when no gross lesion is available for biopsy.

The interpretation of the findings in terms of the indications for specific types of treatment has been the source of much study and argument. The concept that a cancer which is apparently superficial may be safely treated either by conization alone as described above or by simple removal of the uterus has been widely accepted. That the former represents a much too dangerous gamble seems clearly established. Simple removal of the uterus apparently offers a much greater chance of permanent cure of an apparently superficial cancer. It has been established without question, however, that the cure rate is not complete. This raises questions as to the desirability and effectiveness of more radical treatment and the circumstances under which it might be justified.

The Department of Obstetrics and Gynecology at the University of Minnesota has been attempting to obtain information which may be applicable to such decisions. There is a relatively inactive form of the cervical cancer which can be recognized by examination with the microscope. It is unlikely that such cancers have spread beyond the surface, and they are being treated by simple removal of the uterus. When the cancer is made up of actively reproducing cells in masses on the surface or into glands; when there is a question as to whether microscopic invasion of the underlying tissue has occurred, or when the cancer extends to the cut margin of the cervical cone and so is in an unknown superficial or invasive state in the remaining tissue, either more radical forms of surgery or irradiation with x-ray and cobalt^{60} and radium have been used in the hope of increasing the cure rates. The effectiveness of these is also not yet established, but information is being collected. Various types of radical surgery are being tested.

John L. McKelvey, M.D.†
Minneapolis, Minnesota

*Presented at the Minnesota State Medical Association Meeting in Duluth, May 15, 1967.

†Department of Obstetrics and Gynecology University of Minnesota Medical School.

Suicide*

THE RIGHT "to be or not to be," isn't that the question? Each man destroys himself in his own unique way, albeit time factors and methods of accomplishment vary. Besides outright self-destruction, we have many formes frustes† of suicide, as seen in alcoholism, addiction, self-mutilation, malingering, accident-proneness, polysurgery, and even smoking. All interest us, all involve us, all concern us, all violate us. It is fruitless to think we can deny man's right, choice, or need to destroy himself. Our basic obligation as physicians is to offer the patient time for reflective reconsideration under different circumstances. This is our responsibility to our fellow man, and no more.

Richard M. Steinhilber, M.D.
Rochester, Minnesota

*Maris, Ronald: Suicide. Minnesota Med 51:723, 1968.

†See Test Your Word Score Page 1213.

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Precautions: Electrolyte abnormalities may be aggravated or produced. Caution is important during prolonged or intensive therapy and when salt intake is restricted. Hypokalemia has been mild and infrequent, and other electrolyte abnormalities rare. The possibility of potassium depletion and its toxic sequelae must be kept in mind, particularly in cirrhotics and patients receiving digitalis. As a preventive measure the use of foods rich in potassium, such as orange juice, may be desirable. Although not a thiazide, HYDROMOX may possess certain characteristics of the thiazides. They have been known to cause jaundice with liver involvement and pancreatitis; hematological complications such as purpura with or without thrombocytopenia and leukopenia (neutropenia); increases of serum uric acid; decreased glucose tolerance as evidenced by hyperglycemia and glycosuria thus aggravating or provoking diabetes mellitus and azotemia in patients with renal disease; photoallergy. Discontinue use a few days prior to elective surgery. When added to a regimen that includes ganglionic-blocking agents, the dosage of these latter preparations should be reduced. Also reduce dosage when one or more of these antihypertensive agents is added to an established HYDROMOX regimen. Contraindicated in anuria. Observe for possible hematologic complications.
Side Effects: Skin rash; gastrointestinal disturbances (chiefly nausea), weakness, dizziness. These seldom require cessation of therapy, and can be relieved by reducing dosage or correcting electrolyte imbalance.
Warning: Enteric coated potassium tablets have been implicated in small bowel lesions and should be used only when adequate dietary supplementation is not practical.

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Irregular Blood Group Antibodies

In an Eastern newspaper in an editorial entitled "Human Blood Giveth or Taketh Away," the writer called attention to the untimely death of a 30-year-old married woman, following an emergency appendectomy and a single blood transfusion. The article pointed out that this tragedy was not due to lack of surgical skill but rather to a major blood-group incompatibility, despite the fact that both donor and recipient were group O, Rh positive. The woman's blood contained so-called irregular antibodies incompatible with the donor's cells.

With increasing knowledge of blood-group systems, it truthfully can be said that every time a person is transfused he is exposed to some antigenic factor or factors which his body will identify as foreign and to which it may build up antibodies. To the surgically oriented specialist, the problem of irregular blood-group antibodies has become of increasing interest.

We might ask ourselves three questions:

What Are These Irregular Antibodies?

We are all familiar with the naturally occurring antibodies (anti-A and anti-B) in blood serum, for they form the basis of all blood typing. To acquire unnatural or, to use a more exact term, "irregular antibodies," we must have foreign particles or antigens introduced into our hematologic system. Our rejection mechanism protects against such intrusion by the development of irregular antibodies. Serologists are familiar with more than 100 such antigens which, if introduced, are capable of provoking such an antibody response. Once the response has been initiated, these antibodies remain forever lurking within the serum.

Fortunately, a large number of these known antigens have very limited potential for antibody formation, and their ability to stimulate antibody production depends on their incidence in the population, the amount of antigen introduced, and the individual's capability of antigenic response. Once the response has been evoked and the antibodies produced, their capability of destroying subsequent cells carrying such antigens is great, and blood-group incompatibilities exist. The subsequent finding of compatible blood donors whose erythrocytes lack the corresponding antigen may then become extremely difficult when time is short and additional transfusions become necessary.

How Are These Antigens Introduced?

There are but two avenues: transfusions and pregnancy. Almost every Rh-negative woman will have introduced into her circulation during pregnancy fetal cells which, if carrying the Rh as well as other antigens, will be capable of initiating this antigenic response. Fortunately such a reaction will also be influenced by her blood type, for if her blood is incompatible with her infant's blood, that is, if an Rh-negative woman has anti-A or anti-B antibodies in her plasma, it is unlikely that anti-Rh antibodies will be initiated by the Rh-positive cells of a group A or a group B infant. Transfusion recipients do not fare so well. In 1966 there were 6,000,000 blood transfusions administered within the United States, with a mortality rate equal to that of appendicitis. Incidentally, there were, in addition to hemolytic deaths, deaths due to hepatitis acquired from transfusion. The danger as well as the therapeutic value of transfusions must be constantly emphasized. In addition, each transfusion inadvertently introduces many known antigens which are likely to cause an antigenic response.

Can Irregular Antibody Formation Be Avoided?

Because of the great morbidity and mortality associated with hemolytic disease of the newborn, much has been learned about the Rh factor and its antibodies. Some of this knowledge may be adaptable to other fields of medicine in the future. Today, all Rh-negative individuals receive Rh-negative blood, leaving pregnancy the remaining stimulant to the development of Rh antibodies. Approximately 13% of Rh-negative women are mar-

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*As shown by *in vitro* studies.
1. Crunden, A. B., Jr., and Davis, W. A.: Am. J. Obst. & Gynec. *65*:311 (Feb.) 1953.



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ried to Rh-positive men, but since to the three admonitions of the marriage covenant (love, honor, and obey) we cannot add a fourth (be Rh negative), little more can be done to further reduce the overall perinatal mortality of eight to 10%.

Two factors have recently influenced the approach to eradication of this one irregular antibody. The first has been the demonstration of the repeated ability of fetal cells to penetrate the placental barrier, thereby entering the hostile environment of the maternal serum and stimulating antibody production. Fetal cells can be demonstrated by elution methods during almost every pregnancy, the greatest shower coming with the delivery itself. The second factor is the knowledge that when an excess amount of antibody is presented coincidently with a corresponding antigen, no active immunity develops: that is, passive immunity protects against active immunity.

Thus, if an Rh-negative woman who has an Rh-positive fetus with a blood group compatible with hers is given high-titer anti-Rh gamma-globulin immediately after delivery and before active immunity has developed, she will remain immune and never develop irregular antibodies for the Rh factor. Obviously, this same precaution will have to be repeated with each pregnancy. In some 1,000 pregnancies protected in this manner, not a single irregular antibody has developed. This may be the first step in solving other rejective mechanisms, such as those encountered in unsuccessful organ transplants.

Unfortunately, no such approach has as yet been demonstrated for protection against other antigens inadvertently introduced either during pregnancy or with transfusions. Until such hazards are eliminated, we must agree with the Eastern editorial writer in saying, "blood giveth or taketh away," and should add parenthetically, "it is many times more noble to give than to receive."

Edward A. Banner, M.D.*
Rochester, Minnesota

*Mayo Clinic and Mayo Foundation: Section of Obstetrics and Gynecology.

Postural Vertigo

SELDOM DOES a day pass in which the general physician or otologist does not see a patient who complains of postural vertigo. The features of the condition have been succinctly presented by Dr. Lindsay.* He points out that a few well-directed questions will usually identify this type of vertigo and that the production of positional nystagmus by postural testing gives objective proof of the disorder.

For an exhaustive treatise on the subject the reader is referred to the work of Barber.[1]

Neuro-otologic investigation including routine postural tests, caloric vestibular tests, and both pure-tone and speech audiometric examinations should be done in all cases of postural vertigo. In the cases with findings which do not suggest a need for more extensive examination to rule out specific central nervous system disease or labyrinthine disorder, a diagnosis of benign paroxysmal vertigo is made. These patients are informed that their condition is not serious and that it can be expected to subside in a few months. The postural vertigo may never return but in many cases a similar episode, lasting a few months, may occur in the future. Some patients, unfortunately, continue to have postural vertigo indefinitely.

A useful drug is a combination of nicotinic acid, 50 mg, and meclizine hydrochloride, 12.5 mg, taken four times daily for three months. If the symptoms are still present after this, the drug is continued indefinitely. Follow-up examination in four to six months, including audiometric and caloric vestibular tests, should be done in every case to avoid the possibility of overlooking progressive disease.

Jack L. Pulec, M.D.
Rochester, Minnesota

*Lindsay, John R.: Postural Vertigo. Minnesota Med. 50: 1013, 1967.

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1. Barber, H. O.: Positional Nystagmus, Especially After Head Injury. Laryngoscope 74: 891, 1964.



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Precautions: In suspected staphylococcal infections, perform proper laboratory studies including sensitivity tests. If overgrowth of nonsusceptible organisms occurs (constant observation is essential), discontinue penicillin and take appropriate measures. Whenever allergic reactions occur, withdraw penicillin unless condition being treated is considered life threatening and amenable only to penicillin. Penicillin may delay or prevent appearance of primary syphilitic lesions. Gonorrhea patients suspected of concurrent syphilis should be tested serologically for at least 3 months. When lesions of primary syphilis are suspected, dark-field examination should precede use of penicillin. Treat beta-hemolytic streptococcal infections with full therapeutic dosage for at least 10 days to prevent rheumatic fever or glomerulonephritis. In staphylococcal infections, perform surgery as indicated.
Adverse Reactions: (Penicillin has significant index of sensitization): Skin rashes, ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; serum sickness-like reactions, including chills, fever, edema, arthralgia and prostration. Severe and often fatal anaphylaxis has been reported (see "Warnings").
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Intrauterine Fetal Transfusion for Severe Erythroblastosis*

THE NUMBER of cases of erythroblastosis severe enough to require treatment of the fetus before birth is very small. Babies affected by any degree of Rh disease are relatively uncommon, occurring only about once in 120 pregnancies. Some are so mildly affected that they require observation only, but no active treatment. Most of the others can be successfully treated by exchange transfusion of blood after birth at full term. Because some are so severely affected that they would die in utero before the end of the pregnancy, labor sometimes has to be induced prematurely in order to prevent further deterioration and to permit treatment by exchange transfusions.

However, in about 8% of these affected pregnancies, or about one in 1500 of all pregnancies, the fetus can be expected to die before 32 weeks' gestation, eight weeks before term. We do not dare to induce labor earlier than this because of the combined risks of prematurity and erythroblastosis. This is a problem which arises infrequently, but to the woman involved it is a very serious one indeed. In most cases she has already lost several pregnancies and therefore realizes that she has practically no hope of ever having a live baby.

The outlook for such patients has been changed since late in 1963 when a method was devised for treating these otherwise hopelessly affected fetuses by blood transfusions before birth. The aim of this procedure is to try to keep the fetus alive until such a stage of pregnancy is reached at which the risk of prematurity is no longer excessive.

The procedure is carried out in the x-ray department of a hospital. Although the mother is given fairly heavy sedation to keep her and her fetus quiet, she is not given a general anesthetic for the procedure. After localizing the fetus as accurately as possible, a local anesthetic is injected into a small area of the mother's abdomen. A large needle is inserted through this anesthetized area into her uterus and, hopefully, into the abdomen of the fetus. A pliable plastic tube is passed down the bore of the needle and the needle withdrawn quickly so that the fetus will not injure itself if it moves. Further x-rays are taken to make sure that the tube is in the right position, namely, in the abdominal cavity of the fetus. Red blood cells from an Rh negative donor which will not be affected by the Rh disease are then injected through the tube. The mother is kept quiet in hospital for at least 48 hours to reduce any possible tendency for her to go into labor because of the irritation of the uterus. The procedure may have to be repeated several times until the fetus is mature enough to permit premature delivery and extrauterine treatment by exchange transfusions.

Since January, 1964, more than 130 intrauterine fetal transfusions have been given to more than 63 fetuses in Winnipeg, Canada. Twenty-six of these are alive today. Although it was frequently difficult to make a definite diagnosis of the cause of death in the cases which were lost, we think that most of them died because of the severity of their disease when fetal transfusion was first attempted. We estimate that the operative mortality, i.e., the risk of a fetus dying as a result of a transfusion, is about 15%. However, in the past 18 months our operative mortality has been only about 7%, probably due to the increased experience and improved skill. Obviously, in such complicated maternity cases, there are also risks to the mother.

Intrauterine fetal transfusion offers at least some hope to any woman no matter how bad her past obstetric experience or how strong her Rh antibodies are. Because of the obvious risks and difficulties involved, the procedure should be carried out only in well-equipped centers prepared to deal with all possible complications. Even in such centers under the best possible circumstances the operation is very far from the ideal answer to this problem. Recent developments give rise to hope that it will soon be possible to prevent Rh negative women from developing antibodies at all. If this materializes, most of our present methods of treatment, including exchange transfusions and intrauterine fetal transfusions, will become obsolete.

Rhinehart F. Friesen, M.D.†
Winnipeg, Manitoba, Canada

*Presentation at the Minnesota State Medical Association Annual Meeting in Duluth, May 16, 1967.

†Obstetrics and Gynecology, University of Manitoba.

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Letter to the Editor

Professor Lenggenhager and Dr. Stirnemann send you their very best greetings, and we all want to thank you again most sincerely for the opportunity which you have offered us to show our American colleagues what is going on in medicine here in Berne. The Department of Education was also very happy about the Berne issue of your Journal and look forward to their 100 copies. The rising number of students pose great problems in this country with respect to financing the universities and the Berne issue will give them a splendid opportunity to show some returns on their investments—so you have really done medicine here in Berne a great service for which we owe you our sincere gratitude.

P. Lundsgaard-Hansen, M.D.
University of Berne, Switzerland

EDITOR'S NOTE: The University of Berne, Switzerland, Issue of MINNESOTA MEDICINE will appear in December or January. Your Editor and Professor Lenggenhager were fellow students under Professor de Quervain a number of years ago.

Test Your Word Score

Apneustic—*prolonged inspiration with short expiration* (page 1177).

Formes frustes—*an arrested form of disease* (page 1205).

Poikilothermia—*variation in temperature in accordance with surroundings* (page 1240).

Agnosia—*inability to recognize* (page 1251).

Analeptic—*restorative remedy* (page 1275).

Ipsilateral—*on the same side* (page 1282).

Thomas J. Kinsella, M.D.

Dr. Thomas Kinsella, Minneapolis thoracic surgeon, took this unusual shot of Mt. McKinley in early June, 1967. He and Mrs. Kinsella were on a bus-boat tour of Alaska and had stopped at Mt. McKinley National Park where this beautiful picture was taken. Usually Mt. McKinley is enshrouded in a blanket of white clouds.

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Adverse Reactions: Drowsiness; dry mouth; nasal congestion; constipation; amenorrhea; miosis; mild fever; weight gain; hypotensive effects, sometimes severe with I.M. administration; epinephrine effects may be reversed; dermatological reactions; parkinsonism-like symptoms on high dosages (in rare instances, may persist); lactation and moderate breast engorgement (in females on high dosages); and less frequently, cholestatic jaundice (use cautiously in patients with liver disease). Adverse reactions occurring rarely, include: mydriasis; agranulocytosis; skin pigmentation; epithelial keratopathy; lenticular and corneal deposits (after prolonged substantial doses).

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The Editor's Soliloquy

Health Maintenance—Ridiculously Simple

The best medicine on earth is that which provides continuous good health. Such medical care can be had! And free at that! To have and to hold optimum health is so simple that it seems almost too elementary to discuss; yet, paradoxically, to attain ideal physical and emotional well-being is so phenomenal an achievement that only a few rare individuals can demonstrate the self-discipline required to maintain "a sound mind in a sound body."

If those hypochondriacs who complain of aches and pains, fatigue and malaise, worries and apprehensions, would accept the doctor's sound advice, when he wisely declines to supplement it with a needless operation or a written prescription, they would require no tranquilizers for "nerves," no analgesics for "headaches," no antacids for "burping and heartburn," no colagogs for "dyspepsia," no laxatives for "temperamental bowels," no emulsions for an "irritable colon," and no hypnotics for "insomnia." No surgery or medication whatsoever is necessary for those innumerable spectral disorders men and women subconsciously devise to parry the petty problems and crises of life.

It is these residual traces of inadequacy, inferiority, conflict, aggression, and hostility that generate hypochondriasis in the emotionally frustrated, the maritally dissatisfied, the socially maladjusted, the economically disgruntled, whose numerous maladies, eternal fatigue, overweight and lack of physical trim are not signs of organic disease but symptoms of unsuccessful compromise with the facts of life. They comprise the spectrum of imaginary morbidities for which there can be no specific medical cure and no operative relief; and they afflict chiefly the middle-aged, who fill the doctors' offices in the fond hope that the physician can do for them what they are failing to do for themselves.

Their persistence in seeking medical aid would be heroic, if they were Galahads in search of the Holy Grail! In their quest for palliation they become gullible prospects for the advertisers' slick blurbs and the cultists' fraudulent claims, a vast and lucrative field of exploitation which the conscientious and honorable physician declines to enter.

In contrast to these neurotically afflicted middle-aged folks the younger generation, whatever their frailties and deficiencies appear to be comparatively immune to the countless functional disorders so common to their elders. But the physician who tactfully recommends to his patient that she restore her body and mind to the robust physical and emotional integrity of youth is met with the impenetrable resistance and recalcitrance of a thousand and one excuses—excuses and more excuses! She won't forfeit her alibi! She wants the magic elixir! She cannot accept the fact that the preventive maintenance of physical trim and good health and a return to the fresh glow and resiliency of youth is the simplest therapy for the prevention and elimination of a host of functional maladies which she has construed as organic disease.

It does require superlative self-discipline and that is the difficulty.

Carl O. Rice,M.D.

Old Doc Hess says: Why should an old widower get married again and make another girl miserable when he can stay single and make many girls happy?

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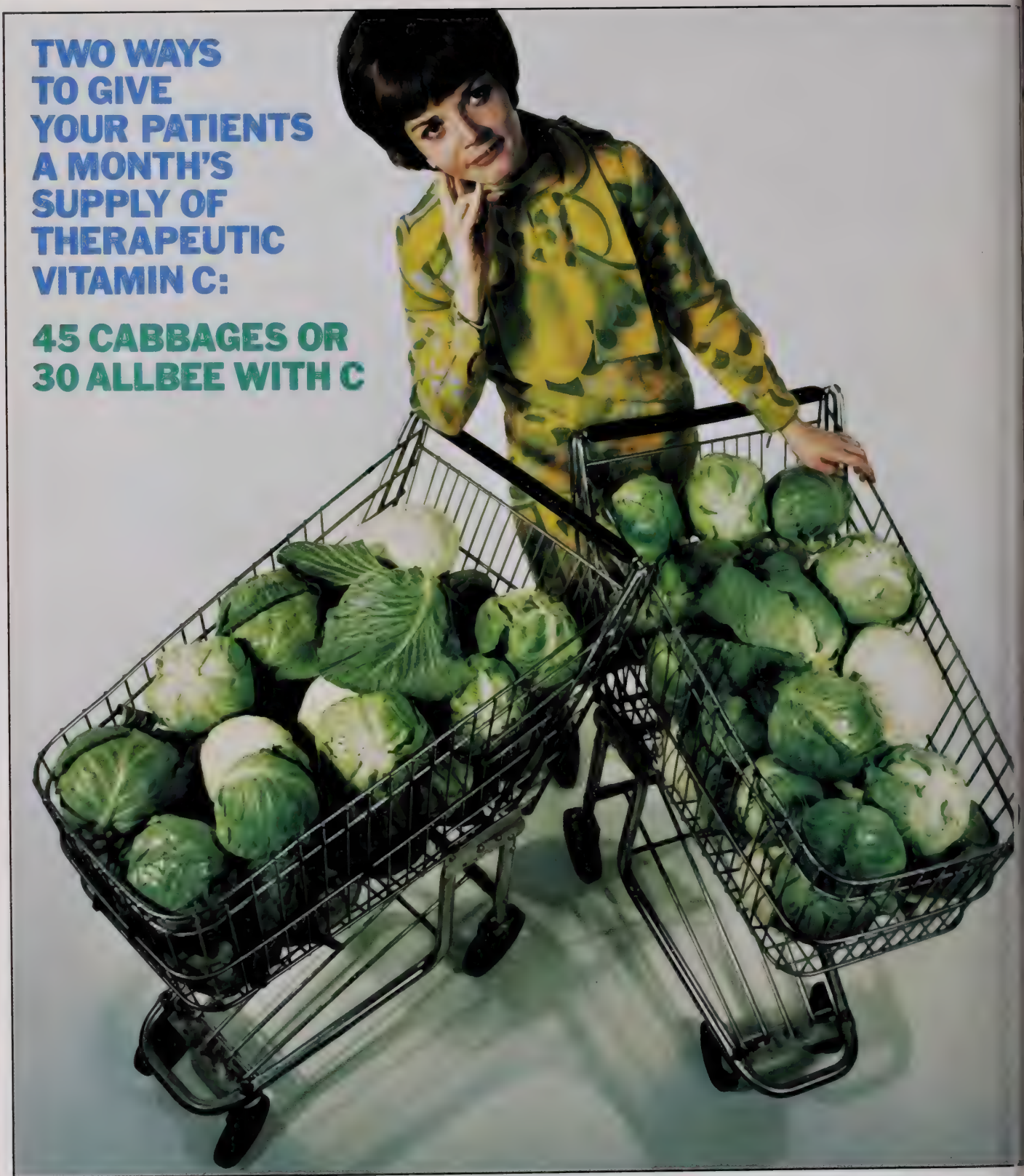
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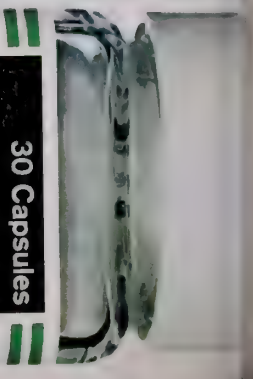
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Acute Viral Encephalitis and Post-Infectious Encephalomyelitis

Emergency Therapy*

MICHAEL E. BLAW, M.D.†
Dallas, Texas

THIS REPORT IS primarily concerned with the treatment of acute viral encephalitis and acute post-infectious encephalomyelitis; however, it should be emphasized that the differential diagnosis is often quite broad. Of particular concern, especially in children, is the specter of exposure to exogenous toxins. In the final analysis the immediate diagnosis and subsequent appropriate emergency therapy depends upon critical appraisal of the history and physical examination.

Since for the most part specific chemotherapy for both viral encephalitis and post-infectious encephalomyelitis is not available, discussion of treatment will necessarily be centered about supportive care and complications. Although the pathological hallmark of viral encephalitis is one of diffuse inflammation of the nervous system, whereas post-infectious encephalomyelitis is characterized by symptoms consequent to disseminated perivenular demyelination, in many respects treatment overlaps. In the discussion to follow, therapy for both processes will be presented in common, recognizing that the application to any given patient depends on the severity and extent of these exceedingly variable pathological processes.

Supportive Treatment

Eliminate Stimuli

Early in the clinical course, particularly with encephalitis, the patient may be hyperexcitable, reacting violently even to the most innocuous environmental stimulation. As a consequence, a room should be chosen which is as far removed from the hubbub of the ward as possible. The blinds should be drawn and the room maintained in subdued light. Barbiturates may be required to sedate the severely agitated patients. Special nurses are indicated until the clinical course stabilizes.

*Presented at the Continuation Course in Neurological Emergencies sponsored by the University of Minnesota, Minneapolis, November 8, 1967.

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Minimize Fluid Intake

Although on admission the patient may have only minimal symptoms, progression can be very rapid. In the acutely hospitalized it is probably judicious to withhold oral feedings and initiate intravenous fluids until a clear picture of the patient's clinical course is obtained. Cerebral edema may play an important role in both mortality and residual morbidity, particularly in viral encephalitis; therefore, intravenous fluids should not exceed maintenance. Once the patient has stabilized, tube feeding, soft bland diets or regular diets can be initiated as circumstances dictate.

Airway

An unobstructed airway is better therapy than an oxygen tent. Pharyngeal suction should be used liberally. If an adequate airway cannot be maintained, tracheostomy is indicated. Mechanical supports for respiration may be required. Urinary retention occurs quite commonly, requiring catheterization.

Cooling

The presence of fever increases metabolic demands and may contribute to the associated cerebral edema. The patient's clothing should be removed and the temperature of the room lowered to approximately 65°. If air conditioning is not available, fans should be used to provide adequate circulation of air. Salicylates may be employed when practical. A cooling blanket can be used when the above means fail, but shivering may reduce the benefit derived therefrom. However, phenothiazines can be used to control shivering, but care must be taken not to produce hypotension.

Treatment of Complications

Convulsions

Convulsions, both generalized and focal, often occur during the clinical course of both diseases. When present they complicate nursing care, potentiate the associated cerebral edema, and increase the likelihood of secondary problems such as aspiration pneumonia. Phenobarbital and dilantin may be used for seizure control, but care must be taken in titrating the anticonvulsants against the seizure activity so that excessive central nervous system depression does not occur. If hepatic disease is present, phenobarbital should be given in preference to dilantin. The latter requires the liver for detoxification. In the presence of complicating renal disease, dilantin should be employed, since phenobarbital for the most part requires normal renal function for excretion.

Cerebral Edema

Cerebral edema and its attendant increased intracranial pressure are prime determinants in the ultimate prognosis; treatment of this will be dealt with in another part of the symposium. However, it should be noted that steroids, although beneficial in reducing the increased intracranial pressure associated with tumors, may not be effective in the edema associated with viral encephalitis. Of the hyperosmotic agents currently in use, glycerol has some obvious advantages[1] as it can be given by mouth and is rapidly metabolized. Toxicity is minimal and there is less tendency for rebound edema. Glycerol is given in an initial dose of 2 gm/kg with 0.5 gm/kg every four hours. A 50% solution in 0.9% saline is used. In the conscious patient, lemon juice can be added to ameliorate the sweet taste.

Antidiuretic Hormone

The syndrome of inappropriate antidiuretic hormone secretion occurs under a variety of circumstances, including certain malignancies, pulmonary disease, surgical anesthesia and a number of neurological diseases such as viral encephalitis.[2] The syndrome is defined by (1) the presence of decreased serum sodium concentrations and serum osmolarity, (2) continued sodium excretion with relatively increased urine osmolarity, and (3) no evidence of fluid volume depletion or abnormal renal or adrenal function. In the presence of inappropriate anti-diuretic hormone secretion, even maintenance levels of intravenous fluids can lead to progressive water intoxication. Fluid restriction below maintenance levels (500-700/m^2) is indicated. Inappropriate anti-diuretic hormone secretion occurring during acute viral encephalitis is usually transient.

Steroid Therapy

Both basic virological and clinical studies suggest that steroids are not effective and indeed may well be contraindicated in acute viral

encephalitis.[3,4] However, considerable literature has developed relating to the use of steroids in post-infectious encephalomyelitis. The initial reports were most encouraging. More recently, controlled studies, both retrospective[4,5] and prospective,[6] have indicated that steroids do not alter either the mortality or morbidity of post-infectious encephalomyelitis.

The Future of Viral Chemotherapy

In the dawn of knowledge related to viral infection it was hoped that eventually a single anti-viral agent could be developed which would serve as a universal antidote but in the light of present day information it has become increasingly apparent that such a therapeutic agent is not likely to be forthcoming. This is a consequence of the fact that each virus is a distinct entity with its own unique structure and the capacity to induce in the host cell enzymes particular to itself. Nevertheless, the search for effective agents is ongoing.[7] Three such anti-viral agents have attracted considerable attention.

Host-Cell Specificity

Interferons are basic polypeptides induced in the host cell by viral particles. Although interferons lack viral specificity, there appears to be strong but not absolute host-cell specificity. This and the fact that they appear to be effective only within the first few hours of an infection limit their clinical utility.

Prevention

Adamantadine (Symmetrel) is an agent which prevents the penetration of the virus into the host cell; but, because it does not affect the virus after penetration, its use is most likely to be in prevention rather than cure.

Antimetabolite

Idoxuridine is an anti-metabolite effective against some deoxyribonucleic acid viruses. Clinically it has been very effective when applied topically in patients with keratoconjunctivitis due to herpes simplex. It has also been employed systemically in a few patients with herpes simplex encephalitis.[8] These initial case reports are indeed encouraging.

Whether or not idoxuridine proves effective in herpes simplex encephalitis, it is apparent that anti-viral agents will be developed that are specifically tailored to individual viruses. Unless there is parallel development of laboratory procedures allowing for specific viral diagnosis early in the course of the disease, we may find ourselves in a position of having at our fingertips a variety of therapeutic agents but handcuffed by our inability to select the proper drug.

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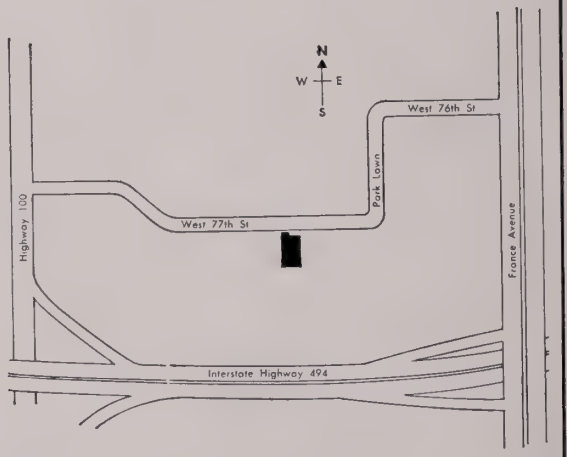
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Major Motor Seizures*

FERNANDO TORRES, M.D.†
Minneapolis, Minnesota

Most texts and monographs dealing with epilepsy start with a reference to historical reports of epileptic attacks and their implications according to the time and type of culture involved. For many centuries the only form of convulsive disorder recognized as epilepsy was the major motor seizure, and its description used in ancient times is still valid.

Major Motor Seizures

A major motor seizure frequently starts with a cry, produced by the violent expiration associated with contraction of thoracic and diaphragmatic muscles. The subject may lose consciousness at the onset. Tonic and clonic convulsions follow, but either phase may be absent. There is foam at the mouth, and there may be incontinence of urine and sometimes also of feces. At the end of the convulsion there is a more or less prolonged period of apnea, terminated by a long inspiration. In most instances, the patient starts moving and talking a few minutes later. There is, however, a period of confusion of variable duration, during which there is only incomplete recovery of consciousness.

Because of the different mechanisms involved and the implications for prognosis and treatment, it is advisable to restrict the term "grand-mal" to major motor seizures which are generalized from the onset.

Focal Seizures

Any focal seizure may become a generalized convulsion, but it is important to distinguish between motor primary and secondary generalized seizures. The former is not preceded by aura because it is generalized from its onset; the latter may or may not be preceded by a warning. The aura is absent when the focal discharge spreads rapidly and consciousness is affected very early in the sequence of events.

Differentiation

Clinically it may be difficult to distinguish be-

* Presented at the Continuation Course in Neurological Emergencies sponsored by the University of Minnesota, Minneapolis, November 8, 1967.

† Professor of Neurology, University of Minnesota Medical School.

tween major motor and focal seizures even after careful questioning of the patient and the relatives, especially in cases of rapidly spreading focal seizures. It is important to inquire not only about aura, but also about any postictal symptoms that may give a clue as to the focal nature of the seizure. The electroencephalogram is frequently helpful in questionable cases. In effect, the individual who suffers from grand-mal seizures will have a normal or only mildly abnormal electroencephalogram during interictal periods and, in the rare cases when a seizure can be electrically recorded, it is possible to see its generalized onset. On the other hand, patients whose convulsions start focally will usually have a significantly abnormal interictal electroencephalogram, and frequently one or more foci of abnormality may be detected.

Propagation

Propagation is a crucial factor in seizure mechanisms, since clinical manifestations may be absent or may become increasingly important according to the capacity of spread of an irritative activity. The initially focal epileptic phenomenon may spread in three ways: (1) following long fiber paths within the hemisphere; (2) projecting to homologous areas of the opposite hemisphere via the corpus callosum or the anterior commissure; (3) propagating along corticothalamic pathways and from the midline structures back to the cortex, bilaterally, and down the descending fiber tracts.

Generalized Seizures

Generalized seizures from the onset have been called "centrencephalic." This term comprises "grand-mal," "petit-mal" and "myoclonic-akinetic" attacks and was introduced by Penfield,[1] based on a theory according to which a centrally placed structure or set of structures around the brain stem and thalamic reticular systems is responsible for the initiation of these seizures. This would explain their generalized onset and also the lack of abnormalities in the interictal electroencephalogram. In the past few years there have been increasing doubts about the importance of the "centrencephalic" structures in the production of seizures. In effect, only rarely have there been anatomical lesions described in these structures of patients with "centrencephalic" seizures.[2] Also there is much evidence pointing to the relatively high seizure threshold of the thalamus and adjacent areas. Some experiments carried out on cats have shown that generalized seizures electrically and clinically indistinguishable from a centrencephalic attack can be produced with bilateral cortical epileptogenic lesions, as long as the corpus callosum remains intact, and even after destruction of the thalamus, hypothalamus, rostral mesencephalon and rostral hippocampus.[3]

It is known that any normal individual may have a generalized seizure in the presence of appropriate circumstances. Focal seizures, on the other hand, are rarely seen in normals. Fast intravenous injection of metrazol, for example, will induce a grand-mal convulsion in any normal subject. Sudden withdrawal of certain drugs may have a similar effect. And sometimes addition and interaction of several otherwise innocuous stimuli may produce a seizure in subjects with lower than normal threshold.

Thus it can be seen that distinguishing between a grand-mal seizure and a secondary major motor attack has immediate practical importance. This distinction is often very difficult to make, but when it can be made it is helpful in terms of prognosis and treatment. In general, a focal seizure requires an extensive investigation of its cause to avoid missing some progressing lesion that might be treatable and perhaps curable at the onset but not later. The extension and depth of the diagnostic work-up will depend on circumstances inherent in each individual case. Seizures starting after 20 years of age warrant more diagnostic effort than those starting in childhood or adolescence. Focal elements detected either from the clinical history or examination or by the electroencephalogram generally require a more exhaustive work-up than grand-mal convulsions.

Management

One single major motor seizure requires no treatment and its management should be limited to the protection of the patient from injury (falling, biting tongue or lips, etc.) and from other harmful events like aspiration of secretions or respiratory obstruction from the swallowing of dental prostheses. Any anti-

convulsant given during or immediately after the attack will at best prevent its repetition but will not alter the course of the seizure, once it has started. It is imperative, however, that an investigation of the cause of the convulsive attack be started as soon as possible.

In the final analysis, regardless of the depth and thoroughness of the investigation, a large number of cases fail to reveal a sufficient cause for the seizure. But, unless the electroencephalogram is grossly abnormal, the occurrence of one single major motor seizure does not warrant treatment, since once started and even assuming that no more attacks occur, anticonvulsant therapy should be continued for two or three years, and only then should the dosage be gradually decreased.

Furthermore, many individuals never have more than one seizure in their life. Therefore, once the physician is satisfied that he has carried out the investigation as far as his judgement and knowledge tell him is necessary and has still not found the cause, he is justified in waiting while he watches his patient closely. Only in those cases in which there is no way of following the patient or of referring him to a reliable physician is it best to start anticonvulsant treatment. But once this is decided upon, there is no point in doing it halfway; because insufficient dosage will not help but may, on the contrary, produce side effects and other inconveniences attached to prolonged treatment. Once anticonvulsant treatment is started, it should be instituted with a full therapeutic dose and with the prospect of a two to three years' span of treatment. The patient should be warned of the danger involved in sudden withdrawal of anticonvulsants, so that he is fully aware of his own responsibility in maintaining the regularity and adequacy of dosage, as prescribed by his treating physician.

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Life's Speed?

We have cherished and preserved a host of couplets and proverbs from the past, intended to urge our more lethargic forefathers to get on the ball and get some work done. Things like Franklin's classics: "Dost thou love life? Then do not squander time, for that is the stuff life is made of." And, "Never leave that till tomorrow which you can do today." We've preserved the stories about the grasshoppers and the ants. And in sundry and subtle ways we urge young and old alike to work faster and to squeeze each minute a little harder—to make hay while the sun shines, and to save up for a rainy day.

We've learned to abhor laziness, and to judge a man by the number of bathrooms in his home. We've been praised for our achievements and scorned for our failures. And still we crack the whip and drive the tempo faster, while the echo of one small voice lingers in the distance: the contention of the late Mahatma Gandhi that "there is more to life than increasing its speed."*

*James Fisher, M.D.: A Few Buttons Missing, 1951.

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ALFRED UIHLEIN, M.D.†
HILLIER L. BAKER, JR., M.D.†
Rochester, Minnesota

CENTRALLY HERNIATED intervertebral disks can occur in the cervical, thoracic, and lumbar vertebral regions. In the lumbar region they may result from chronic disk degenerative disease or spondylosis, with or without antecedent trauma. In either degenerative disease or spondylosis, compression of the elements of the spinal cord or the cauda equina by a slowly progressive lesion does not produce the severe neurologic deficit that results from an acute lesion. Thus the recovery from the deficit produced by the acute lesion is not as prompt or gratifying as that found with a chronic, slowly progressive, midline disk herniation. Fortunately the incidence of centrally herniated intervertebral disks is small, but such a lesion does produce characteristic neurologic changes.

Cervical

Causative Factors

Centrally herniated disks in the cervical region are encountered most frequently in conjunction with acute trauma or spondylosis.[1-3] A "whiplash" injury may produce cervical spondylosis, with the concomitant production of a centrally herniated soft disk. A "hangman's fracture" of the cervical vertebra may likewise produce an acute centrally herniated disk. This fracture of the cervical spinal column is characterized by a bilateral fracture through the neural arch of the second cervical vertebra, with or without dislocation of the body of the axis on that of the third cervical vertebra.[4]

Early Treatment

When an acute centrally herniated disk occurs in conjunction with trauma to a cervical vertebra, varied degrees of paraparesis or quadriplegia with a fluctuating sensory level is seen early clinically. Unless decompression of the common dural sac by surgical means is not carried out promptly, with the removal

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†Mayo Clinic and Mayo Foundation: Sections of Neurologic Surgery and of Roentgenology.

of the herniated disk, irreparable neurologic deficit may result. This type of decompression should be done under skeletal traction to the skull in order to stabilize the cervical column as much as possible while a posterior decompressive laminectomy or an anterior spinal-cord decompression is being done to avoid further damage to the cord during surgery. If intact, the dura mater should not be opened to facilitate removal of the soft disk material in front of the cord, but rather this material should be removed by use of an adequate bilateral exposure; thus the cerebrospinal fluid surrounding the cord can act as a protective sheath to an already edematous cord, which is the result of trauma due to the central herniation. Removal of disk fragments with an intact dura may prevent undue manipulation of the cord, which could be an important factor in the eventual outcome of surgical intervention.

Surgical Intervention

There are those who advise that surgical intervention in the face of an acute neurologic deficit due to a centrally herniated cervical disk accomplishes little if there is no evidence of a spinal subarachnoid block on lumbar puncture or by myelography with contrast medium. This is not necessarily true. If the validity of these tests is in doubt, surgical exploration can best determine the extent of cord damage. Sometimes the advantages gained from direct observation of the amount of cord compression at surgery outweighs the apparent advantages gained from procrastination. Some believe that skeletal traction alone to the cervical spinal column may reduce an acute centrally herniated disk sufficiently to decrease the neurologic deficit with the passage of time; however, any deterioration in the neurologic examination during a 24- to 48-hour period of observation justifies exploration.

A neurologic examination to determine which cervical nerve roots are primarily involved is essential (Figure 1) so that adequate decompression of the nerve-root sleeves and contiguous spinal cord at the correct level can be done at surgery.[3] The transdural removal of a centrally herniated disk should be reserved only for those situations in which the disk material has ruptured through the ventral dura and presented in the subarachnoid space. A posterior fusion operation should be deferred at this time, because preparation of the bed could damage the cord further either by indirect trauma or by extradural pressure from a clot that results from bleeding in bone secondary to the preparation of the bed for the bone graft.

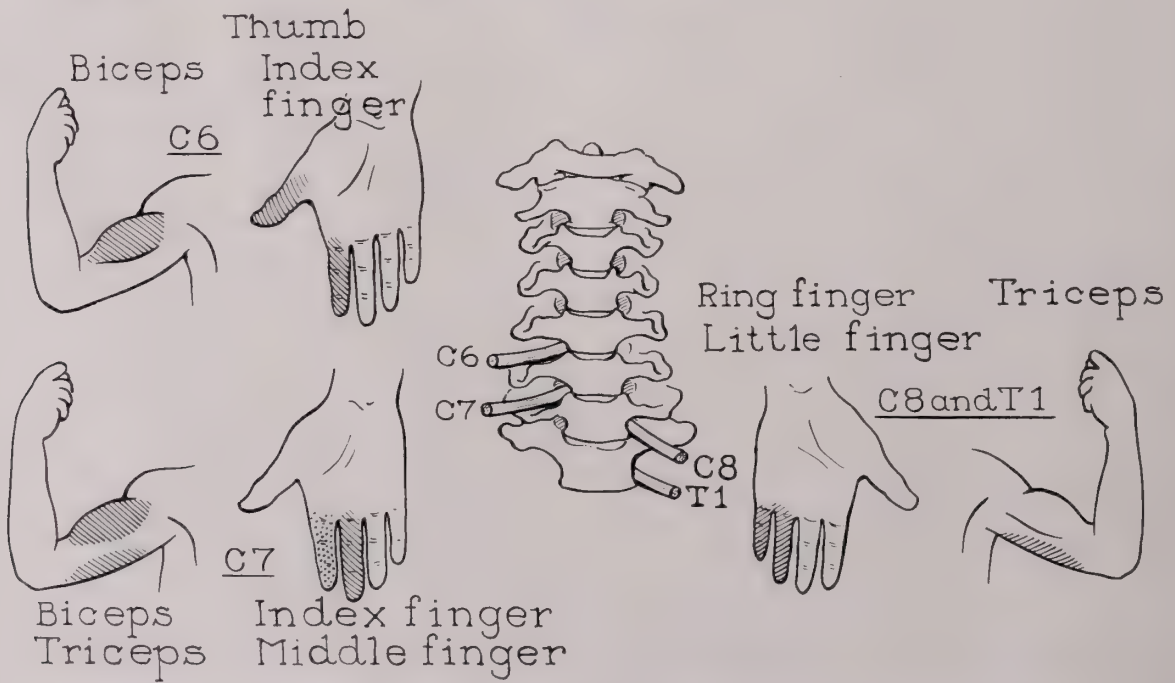


Fig. 1—Diagram of neurologic changes associated with compression of the cervical nerve root.

Thoracic

Progressive Onset of Symptoms

Protrusion of an intervertebral disk in the thoracic region occurs infrequently when compared to protrusions in the lumbar and cervical vertebral column.[5,6] Trauma may or may not be a contributing factor, and protrusions have occurred at every vertebral level. In cases of trauma, the patients may not lose the use of their lower extremities initially, but the progressive loss of sensation or locomotion over a period of time necessitates surgical intervention. Surgery may not result in improvement, but undue delay may produce permanent damage to the spinal cord.

The most common presenting symptoms are pain and numbness associated with some difficulty in locomotion.[7,8] Paresthesias and perverted sensations predominate, and pain may be located in the thoracic or low-back regions.

Objective Finding

Roentgenograms of the thoracic vertebrae may show evidence of calcification of the thoracic intervertebral disk that is producing the symptoms;[9] however, this region of calcification may not be the one that is producing cord compression. Myelography with contrast medium may show a specific defect in the anteroposterior projection at one (Figures 2 *A* and *B*) or more levels (Figure 3) that is characteristic and will exclude the possibility of a cord tumor or other lesion.

The protein level of the spinal fluid may be increased in thoracic-disk protrusions.[6] Sur-

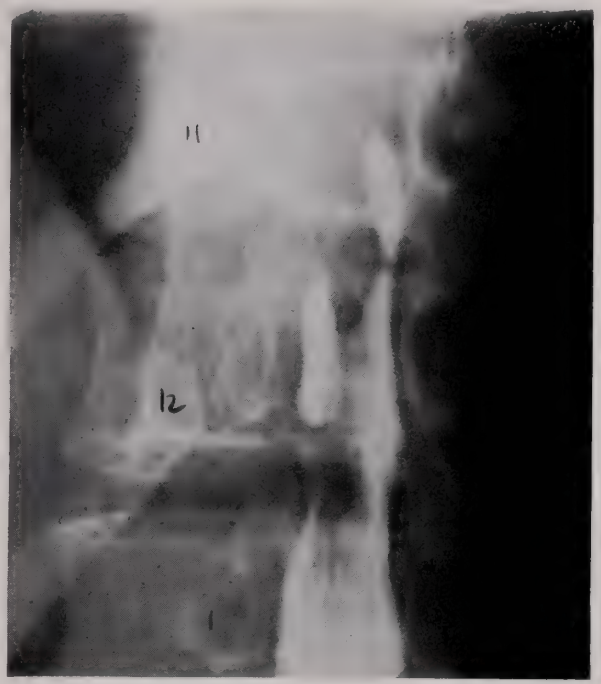


Fig. 3—Multiple defects in contrast-medium column due to centrally protruded thoracic disks.

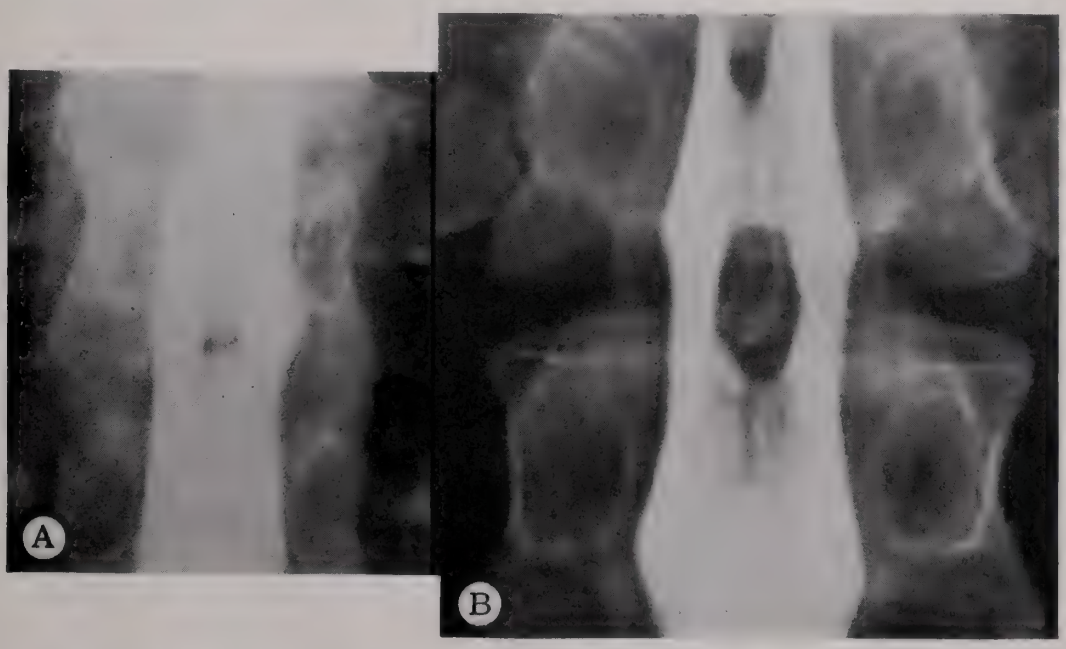


Fig. 2—*A* and *B*, Defect in contrast-medium column due to centrally protruded thoracic disk. (From Baker, H. L., Jr., Love, J. G., and Uihlein, A.: Roentgenologic Features of Protruded Thoracic Intervertebral Disks. Radiology 84:1059, 1965. By permission of The Radiological Society of North America, Inc.)

gical results in these cases may be discouraging because prolonged cord compression has produced irreversible changes. After laminectomy and decompression, the neurologic status may not be altered and may even be worse, as reported by some.[8] A lateral approach to the disk region (costotransversectomy) has been reported[10] as reducing the danger of increasing the neurologic deficit after operation because the cord is in less danger from direct trauma. Nonetheless, the surgical results may be less fruitful than anticipated. Careful patient selection is important.

Lumbar

Centrally herniated intervertebral disks in the lumbar region generally occur below the level of the conus medullaris and compress the roots of the cauda equina; this represents a peripheral nerve type of injury. In acute compression of the cauda equina, the need for surgical intervention should not be questioned. Compression of the roots secondary to trauma to the bone or secondary to a protruded intervertebral disk should be prompt in order to prevent progressive loss of nerve function of the cauda equina. In degenerative disk disease the degree of neurologic deficit cannot be assessed adequately without an accurate patient history and careful neurologic investigation (Figure 4). Progressive weakness, even in the presence of decreasing pain, justifies a positive approach to avoid further motor loss both to the extremities and to sphincter control. Roentgenograms of the lumbar spinal column and myelograms with contrast medium may be required to determine the compression level and to exclude other causes of a cauda equina lesion.[11-14]

Recently Love and Emmett[15] have reported the incidence of prolonged periods of urinary retention in women relieved by the removal of an "asymptomatic," protruded, lumbar intervertebral midline disk.

Comment

The acute compression of the cervical or

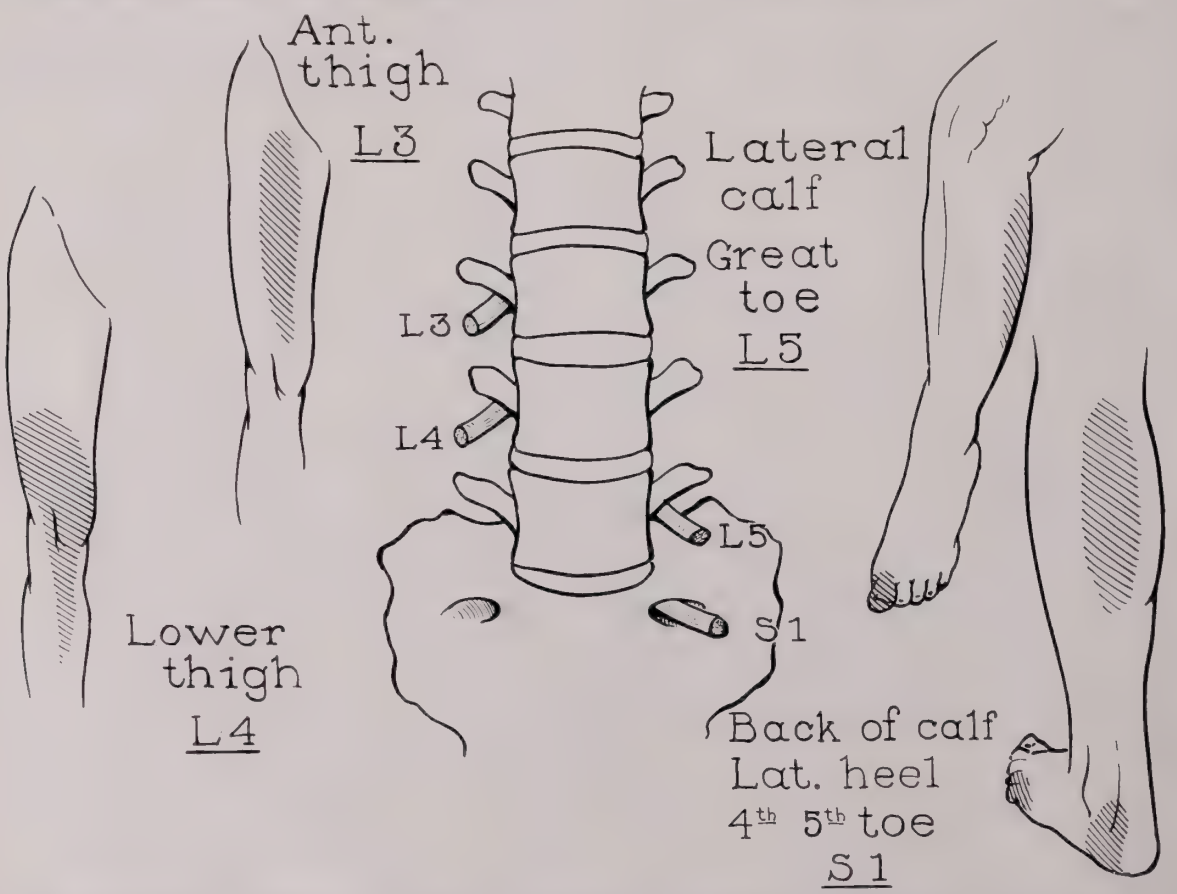


Fig. 4—Diagram of neurologic changes associated with compression of the lumbar nerve root.

thoracic cord as well as the cauda equina by a centrally herniated intervertebral disk may constitute an emergency because of progressive neurologic deficit. Early surgical intervention with decompression of the dural sac and its contents may prevent paraparesis or quadriplegia, depending solely on the amount of cord damage that occurred prior to surgery. This is especially true in lesions affecting the cervical and thoracic regions of the spinal cord.

Considerable difference of opinion still exists in the management of cervical spondylosis, when the degree of cord involvement is slowly progressive. The question revolves around whether decompression of the cord by a posterior translaminal approach, as Scoville[2] has recommended, is preferable to decompression by anterior cervical intervertebral disk removal and fusion.[16] The associated hypertrophic ridges and spurs can be removed more readily by the anterior approach; however, when multiple intervertebral disk levels are involved, the anterior approach has not been as successful as the posterior approach in decompressing the common dural sac. Certainly in midline disk protrusion associated with spondylosis (unless some form of decompression is carried out), a serious quadriplegic neurologic deficit may eventually develop. The ideal surgical approach has not been found. Connolly, Seymour, and Adams[17] in 1965 summarized their experience with anterior cervical fusion as follows: "It is our belief that this operation will gradually find its proper place in the treatment of degenerative cervical disc disease. The results in this carefully evaluated series do not, however, justify the degree of enthusiasm expressed for this operation in some earlier reports."

The taking of a careful history and a neurologic examination in these cases are essential to a correct interpretation of the underlying cause of the patient's complaint. Excellent radiographic studies utilizing tomography and cineradiography may be more informative than contrast-medium myelography or diskography, in both of which correct interpretation may be difficult. The surgeon must not allow these myelographic alterations to predominantly influence the manner of management without correlating these findings with the history and clinical examination.

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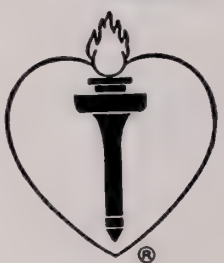
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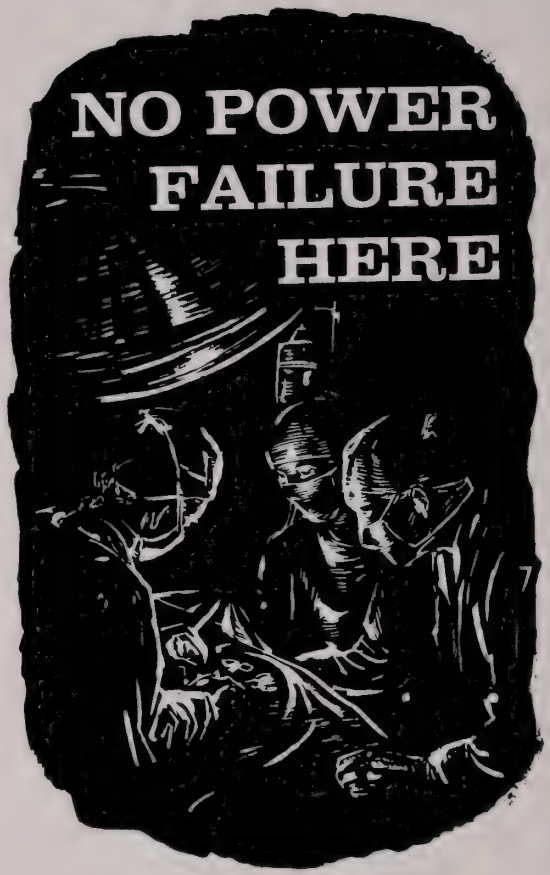
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Spinal Cord Compression Secondary to Neoplasms*

DON M. LONG, M.D., PH.D.†
Minneapolis, Minnesota

A 42-YEAR-OLD MAN was in good health until he noted a dull back pain which appeared after an accident in which his wife was run over and he himself barely escaped injury by throwing himself violently backward. The pain soon localized to the left subscapular area, was continuous, and was accentuated by movement. A diagnosis of traumatic intercostal neuralgia was made. When no relief was obtained by the usual conservative measures, a diagnosis of thoracic aneurysm was entertained. He successively consulted several physicians while becoming progressively incapacitated by pain. He became so irascible that his sanity was questioned, and the pain was thought to be of psychogenic origin. Three years after the onset of pain his left leg became weak. Subsequent paresis of the right leg was followed by loss of sensation and finally urinary retention. Mental symptoms were so prominent that "shock" therapy was advised. Before this step was taken, however, neurological consultation with an eminent neurologist was obtained. Examination revealed a spastic paraparesis of four months' duration with a T-6 sensory level, clonus, hyperactive reflexes, loss of bowel and bladder function and a urinary tract infection. Pain was so severe that the patient could not bear to be moved. A diagnosis of left-sided intraspinal neoplasm in the high thoracic region was made. Referral was made to an equally eminent neurosurgeon. Laminectomy of the T4-T6 area revealed no tumor; however, encouraged by the neurologist, the surgeon extended the limits of the incision and encountered an intradural extramedullary neurofibroma which was totally removed. Within one week recovery of sensation had begun, and one year later recovery of neurological loss was complete.[9]

This illustrative case report of a patient treated by William Gowers and Sir Victor Horseley, which sounds surprisingly current, represents the first spinal-cord tumor successfully diagnosed and treated. Prior to this demonstration of the feasibility of the diagnosis and removal of spinal-cord neoplasms, only 58 cases of cord tumor had appeared in the medical literature. McEwen had successfully performed laminectomies for other disease, but the operation was generally held to be impossible, and the prognosis of spinal-cord tumor was considered hopeless.[3] Following Horseley's surgical feat, such procedures rapidly became routine, and only thirty-seven years later Elsberg was to write a definitive mono-

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graph detailing 100 operative cases and providing much of the clinical information in use today.

Anatomy

The spinal cord lies completely encased within the bony vertebral canal. There are seven cervical, 12 thoracic and five lumbar vertebrae with the five sacral and four coccygeal bodies being fused into separate single bones. Corresponding to these vertebrae are 31 spinal-cord segments and pairs of nerves, eight cervical, 12 thoracic, five lumbar, five sacral and one coccygeal. Since there are eight cervical segments and only seven cervical vertebral bodies, each cervical nerve exits from the spinal column above the vertebra of corresponding number, with the C8 nerve lying between C7 and T1. Beginning with the first thoracic nerve all nerves pass out below the vertebra of like number.[2]

Vertebra vs. Cord Level

Because of a disparity of growth the end of the spinal cord lies between L1 and L2 in the adult. The following rule may be applied to determine the probable level of cord involvement when the region of bony abnormality is known. C1 vertebral involvement means C1 cord involvement. Between C2 and T10 add 2 to the vertebral number to give the cord segment. That is, C4 vertebra means C6 cord, T8 vertebra means T10 cord, and so on. All the lumbar segments lie opposite the spinous processes of T11-12, and all the sacral and coccygeal segments are at L1 and below.[2,5]

Vascular Supply

The major vascular supply of the cord is through the single anterior spinal artery which arises through fusion of paired branches of the vertebral arteries and is reinforced by a varying number of segmental arteries below. In addition, paired posterior spinal arteries follow a wandering course in the posterolateral sulcus, supplying the posterior columns and posterior horns. The anterior two thirds of the cord is supplied by the anterior spinal artery via central penetrating branches or circumferential pial vessels.[2]

The system of vertebral veins is very complex. There are extensive venous channels in and on the cord which communicate with a dense epidural plexus which connects with segmental veins of neck, thorax and abdomen, providing a ready pathway for metastatic or inflammatory disease to reach the intraspinal compartment.[2]

The Afferent System

Localization of cord compression is based primarily upon the effects of this compression on a few major spinal tracts. The afferent systems which are clinically most useful are as follows. The posterior white columns subserve the ipsilateral side of the body and carry *position and vibratory sense* as well as touch. Lesions of this area cause deficits on the same side of the body below. The lateral spinothalamic tract lies in the anterolateral quadrant and carries *pain and temperature sensation* from the opposite side of body. The ventralspinothalamic tract is concerned with *light touch and is also a crossed tract* serving the opposite side of the body. It is found in the anterior white columns. However, it is not the only pathway subserving touch; this modality is probably represented in several different areas and is therefore a less accurate measure of level of involvement than pain sensation.

The Efferent System

Efferent systems of value are the corticospinal and the sympathetic tracts. As neither tract crosses in the spinal cord, lesions produce ipsilateral deficits. The corticospinal tract is located in the posterolateral quadrant. Corticospinal lesions result in *motor weakness, increased stretch reflexes, absent cutaneous reflexes, and extensor toe signs.* Sympathetic interruption produces *loss of sweating* below the lesion, fall in blood pressure and poikilothermia.* Sympathetic fibers are located central to corticospinal and lateral spinothalamic areas and near the junction of posterior and anterior gray horns.[2]

Pathology

Spinal-cord tumors are traditionally classified into (1) extradural, (2) intradural-extramedullary, and (3) intramedullary. Individual tumors have some unique characteristics, but generalities can be induced. These tumors are

*See Test Your Word Score Page 1213.

predominantly found between ages 30 to 60 years, though they occur in all decades. There is no sex differential except with a few specific tumors. There is no site of predilection; most are found in the thoracic region simply because it is longer. Cord tumors are not common, representing about 0.4 percent of autopsies and about two percent of tumors in general; but the increased longevity of cancer patients is steadily increasing the incidence of metastatic intraspinal lesions. Cord tumors are about one-sixth as frequent as brain neoplasms.[1,3,4,8]

Extradural Tumors

Extradural tumors represent about 22 percent of the total of primary spinal-cord tumors, a percentage depending greatly upon the patient population involved. Where cancer incidence is high, the frequency of extradural neoplasms has been reported to be considerably higher.[1] As intimated, the majority of these tumors are metastatic. The most frequent primary lesion is carcinoma of the lung, with breast, prostate, gastrointestinal tract, thyroid and kidney following. Sarcomas, chordomas, and lymphomas of various types complete this list. Chordoma merits special notice since the majority of the tumors arise in the sacral region and attain huge size prior to recognition. They may grow in the extradural space, compressing nerve roots, even reaching the lower spinal cord.

Inflammatory lesions of the extradural space may develop into well-circumscribed abscesses with cord compression. *Granulomas from tuberculosis or syphilis* are no longer common, but fungal granulomas are increasing in frequency. Spontaneous epidural hemorrhage may mimic spinal-cord tumor. The precipitating cause is usually anticoagulation or a blood dyscrasia. If large enough the ridges of cervical osteoarthritis may mimic a spinal-cord neoplasm in symptoms and signs.

Intradural-extramedullary

Intradural-extramedullary tumors usually arise from the leptomeninges and nerve root sheaths. Meningiomas and neurofibromas account for about 85 percent of the group, while this classification of tumors represents about 55 percent of the total of spinal-cord tumors. Arteriovenous malformations, dermoids, and metastatic brain tumors are less common lesions. Ependymomas of the filum terminale (the so-called "giant tumor of the cauda equina") arise from a collection of ependymal cells near the tip of the conus medullaris and are the third most frequent tumors of this group.[3,4,6]

Neurofibromas are the most common tumor and are frequently dumbbell in shape with a large extradural or even extraspinal portion. They are frequently present in association with von Recklinghausen's disease and may be multiple.

Meningiomas are only slightly less common than neurofibromas. They occur most frequently in the thoracic area in women.[5] They may be found at any point but are usually near the exit of the spinal nerve.

Vascular malformations are most common in the thoracolumbar area and are usually both extra- and intramedullary. They may cause symptoms by compression, by thrombosis with cord infarction, or by hemorrhage.

Dermoids are primarily tumors of children. They are usually associated with a lumbar sinus tract, lipoma, or hair patch. It is important to remember that any such external lesion may indicate a tumor and that the tumor may be located at any level from the skin lesion to the conus medullaris. Meningitis is a frequent complication of these tumors.[8]

Intramedullary Tumors

Intramedullary tumors are predominantly gliomas. Nearly 50 percent of these lesions arise in the lumbar region. Ependymoma is the most common histological type; astrocytoma is second; any of the other gliomas may occur as a rarity, with glioblastoma, oligodendroglioma and medulloblastoma being most frequent. Vascular malformations occur as described. Syringomyelic cysts may result from intramedullary gliomas and mimic benign syringomyelia for an extended period.

Signs and Symptoms

It is apparent from the variety of possible lesions that the symptoms and signs of spinal-cord tumors will be equally variable; nevertheless, classifications of constellations of symptoms and signs are possible. The course of these neoplasms is usually slow and con-

tinuous, though acute presentations do occur, as do remissions and exacerbations. There are basically four general methods of presentation and progression, based upon the predominating symptoms with much overlap: (1) radicular pain followed by ipsilateral motor and contralateral sensory loss proceeding to bilateral motor-sensory loss with impairment of bowel and bladder function; (2) unilateral paresthesias with contralateral motor and sensory loss progressing to complete paraplegia; (3) severe back pain of long duration followed by motor, sensory and sphincter disability, and (4) loss of motor function followed by sensory and sphincter disturbances without pain.[3,4] These groups may be further subdivided into *segmental* and cord *compression* symptoms.

Segmental Symptoms

Fortunately the favorable neurofibromas and meningiomas frequently announce themselves by radicular pain, often continuous, increased by straining, and worse at night. The pain may mimic visceral disease, and about 10 percent of patients with intraspinal neoplasms are mistakenly operated upon for an abdominal lesion. Root or anterior horn cell compression may lead to other segmental symptoms; muscle atrophy, fasciculations, loss of reflexes, and radicular sensory loss.

Compression Symptoms

The signs of cord compression are rarely symmetrical; characteristically, impaired motor function on one side and pain-temperature sense on the other are found early. Touch is affected later. The motor loss is typically spastic and greater in flexors than extensors. Stretch reflexes are usually increased; clonus and Babinski signs are present. Proprioceptive or posterior column function is impaired more on the side of greatest cord involvement. Pain and temperature sense and light touch are usually more distally affected, and loss becomes less evident near the level of the lesion. A zone of radicular hyperesthesia may cap the anesthetic area. Sweating is usually decreased below the level of the lesion. Bowel and bladder dysfunction also occurs routinely.[3,4,7]

It is very difficult to clinically distinguish extradural from intradural - extramedullary lesions. However, the differentiation of these two groups from intramedullary tumors is usually possible on the basis of the neurological manifestations.

Intramedullary Symptoms

With intramedullary neoplasms the course is frequently prolonged. Sensory and motor loss may predominate segmentally near the lesion. Perianal sensory sparing is common. Pain is rare. Anterior horn cells are often involved. Corticospinal tract impairment is late. Bowel and bladder dysfunction occurs in the last stages of the tumor development. Spinal block is rare and late.

Extramedullary Symptoms

With extramedullary lesions radicular pain is common, the sensory loss is uniform, motor loss and bladder dysfunction occur early. Spinal block is much more likely to appear at an early stage in the disease.[3,4]

Diagnosis

It should be apparent that the diagnosis of cord tumor is usually suspected from the history and examination. X-rays of the spine may show bony destruction or erosion, loss of pedicles, or widening of the spinal canal. Metastatic tumors commonly destroy bone, and pathologic fractures are common. Myelography is usually necessary to establish the diagnosis. Extradural tumors can be recognized by ragged appearance of the edge of the dye column as it attempts to pass the obstruction. Intradural-extramedullary tumors are usually sharply circumscribed and separate from the spinal cord. Intramedullary tumors present with widening of the spinal cord.[3,4]

Occasionally it will be of value to perform simultaneous cisternal and lumbar punctures to put dye above and below the lesion for complete delineation of upper and lower margins. Finally, it should be remembered that preparations for surgery should be made prior to myelography in any cord tumor suspect, for sudden decompensation following lumbar puncture is not uncommon. Lumbar puncture before myelography is rarely indicated. If it is performed, however, the spinal fluid protein will frequently be elevated. The Queckenstedt test for spinal blockage is of little use in the diagnosis of spinal tumors.

Differential Diagnosis

The list of possible lesions simulating spinal-cord tumor is formidable and far too extensive for complete review. In general terms, infectious myelitis, toxic myelopathy, trauma, vascular disease, intervertebral disc disease, metabolic conditions such as diabetes mellitus, demyelinating diseases, and developmental defects are the major categories to be considered.[7]

Treatment

The treatment of spinal-cord tumors is primarily surgical. Certain tumors may receive irradiation or chemotherapy after operative decompression, but if there is evidence of cord compression surgery must precede other therapies in most instances. Ideally treatment should be instituted while symptoms and deficits are minimal. However, it must be stressed that speed is of the utmost importance once profound neurological loss has occurred. The faster the cord can be decompressed, the better the chance of recovery. Several other factors are also involved in recovery. A long history of slow development of neurological loss is more favorable than a short one. Paraplegia of rapid onset is less likely to recover than a deficit which has taken several days to develop. Complete loss of function is less apt to improve than incomplete. Paraplegia of more than 72 hours' duration is usually hopeless Nevertheless, with any of these histories, no matter how favorable or unfavorable, it is urgent that treatment proceed to give every chance for recovery of function. The aim of treatment is to remove the tumor, relieve pressure on the spinal cord or roots, and alleviate blockage of spinal fluid circulation. Complete removal may not be possible, but unless the latter two conditions are met, improvement is unlikely.

Extradural Tumors

In general, extensive laminectomy with relief of spinal block and cord compression is the treatment of choice. Metastatic tumors should be operated upon to prevent paraplegia unless the patient is terminal with widespread metastases. Only partial excision of the tumor is usually possible. Postoperatively x-ray therapy or chemotherapy is frequently given.

Inflammatory collections are drained and appropriate antibiotics given. The sacral chordomas are a special problem, but with radical excision, cures may be expected. Hematomas simply require evacuation.

Intradural-extramedullary Tumors

The majority of the neurofibromas and meningiomas can be completely removed and so cured. Giant ependymomas of the filum terminale may also be totally excised. If total removal is impossible, then x-ray may benefit the ependymomas. Dermoids are curable lesions; but great care must be taken not to spill the contents into the spinal fluid, for a chemical or bacterial meningitis may develop. The vascular malformations may only rarely be removed totally. Recently it has been shown that ligation of feeding vessels after their identification by selective aortography may benefit these patients. Currently this is being performed only after severe neurological loss which incapacitates the patient. The technique may prove useful in these discouraging cases.

Intramedullary Tumors

These are the most difficult of spinal cord lesions with which to deal. For many years decompression and irradiation with evacuation of cysts was the only effective treatment. However, with the use of two-point coagulation, microsurgery, or the operating microscope, many of these lesions can now be excised without significant spinal-cord damage. In order to totally remove these lesions a two-stage technique is sometimes advantageous. The first stage consists of laminectomy and myelotomy; at the second operation a week or so later, the tumor will often have delivered itself through the myelotomy site, facilitating removal. If removal is incomplete, x-ray therapy is usually given postoperatively.

Syringomyelic or hematomyelic cavities can be drained or opened to allow continued release of contained fluid. X-ray is of no value for syringomyelia unless the cavity is caused by an intramedullary glioma.

Conclusions

In summary, it may be stated that spinal-cord neoplasms characteristically present with two types of symptoms, radicular and cord-

compression.

Extradural tumors are most likely metastatic or lymphomatous.

Intradural-extramedullary tumors are usually neurofibromas or meningiomas.

Intramedullary tumors are commonly ependymomas or astrocytomas.

Whatever the nature of the lesion or the mode of onset of symptoms, once signs of spinal-cord compression appear an emergency situation exists. Diagnosis and therapy must follow as rapidly as possible. Accurate diagnosis requires, in addition to neurological examination, spine x-rays and usually myelography. Prompt surgical excision of the lesion is mandatory if return of function is to be expected. It is worth reemphasizing that in our series of spinal-cord tumors, 41 percent were benign and removable, while an additional 15 percent were potentially curable (Table). This high percentage of curable lesions makes prompt diagnosis and treatment even more imperative.

TABLE
University of Minnesota Spinal-Cord Tumors
(250 cases operated upon)

14%	Meningioma
15%	Neurofibroma
32%	Metastatic
11%	Intramedullary glioma
4%	Arteriovenous malformation
12%	Other benign
12%	Other malignant

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WALLENBERG'S SYNDROME

This syndrome is caused by occlusion of the posterior-inferior cerebellar artery, resulting in sensory and sympathetic disturbances. Cerebellar and paramidal tract signs and evidence of partial involvement of the 5th, 9th, 10th, and 11th cranial nerves are usually seen.

It is most often associated with vertigo which may result in falling. There may be nausea, vomiting, ipsilateral ataxia, muscular hypotonicity, past-pointing, lateropulsion, and other cerebellar signs.

The physical examination may reveal facial paresthesias, homolateral nystagmus, hiccough, dysphasia, dysphonia, dysarthria, and diplopia. Horner's syndrome is almost invariably present.

The syndrome is usually seen in the arteriosclerotic patient. Some patients may recover within a few months, but other patients may be left with neurologic residuals.

Durham, Robert H.—Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

There is a great deal of difference between the eager man who wants to read a book and the tired man who wants a book to read.—Gilbert Chesterton

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Effectiveness: ACHROMYCIN Tetracycline is a crystalline broad-spectrum antibiotic which provides effective therapeutic activity against susceptible microorganisms.

Contraindication: History of hypersensitivity to tetracycline.

Warning: In renal impairment, usual doses may lead to excessive accumulation and liver toxicity. Under such conditions, lower than usual doses are indicated and, if therapy is prolonged, serum level determinations may be advisable. Some patients may develop a photodynamic reaction to natural or artificial sunlight. Those with a history of photosensitivity reactions should avoid direct exposure to sunlight while under treatment. Discontinue drug at first evidence of skin discomfort.

Precautions: Use may result in overgrowth of nonsusceptible organisms. Constant observation is essential. If new infections appear, take appropriate measures. Use of tetracycline during teeth development may cause discoloration of teeth.

Side Effects: Gastrointestinal system—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin—maculopapular and erythematous rashes (a case of exfoliative dermatitis has been reported); photosensitivity reaction, onycholysis and discoloration of nails (rare). Kidney—rise in BUN, apparently dose-related. Hypersensitivity reactions—urticaria, angioneurotic edema, anaphylaxis. In young infants, bulging fontanels have been reported following full therapeutic dosage. This symptom has disappeared rapidly when drug is discontinued. Teeth—dental staining (yellow-brown) in children of mothers given tetracycline during the latter half of pregnancy, and in children given the drug during the neonatal period, infancy and early childhood. Enamel hypoplasia has been seen in a few children. Blood—anemia, thrombocytopenic purpura, neutropenia, eosinophilia. Liver—cholestasis (rare), usually at high dosage. Tetracycline may form a stable calcium complex in bone-forming tissue. If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy.

Average Adult Daily Dosage: One Gm. per day, in 4 divided doses of 250 mg. each. Should be given 1 hour before or 2 hours after meals, since absorption is impaired by the concomitant administration of high calcium content drugs, foods and some dairy products. Treatment of streptococcal infections should continue for 10 days, even though symptoms have subsided.

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Poliomyelitis*

The Bulbar Type

HAROLD H. NORAN, M.D.
Minneapolis, Minnesota

THIS CONDITION actually should be termed the brain-stem type of poliomyelitis since essentially all of the cranial nerves may be involved in various combinations. Involvement of III, IV, V, VI, VII, VIII cranial nerve nuclei is termed the upper cranial nerve type while that of the IX, X, XI and XII is referred to as the lower cranial nerve nuclei type of bulbar poliomyelitis. Actually, any combinations may occur. Involvement of the lower cranial nerve nuclei are the more serious and more important clinically and constitute a typical bulbar palsy.

Poliomyelitis is caused by a filterable virus of three different subtypes. All may produce an acute bulbar palsy. The frequency of the bulbar type of paralytic disease varies from six to 25 percent, but in those with previous tonsillo-adenoidectomies the frequency definitely increases and some bulbar involvement is said to occur in as high as 85 percent of these cases. Pure bulbar involvement is more common in children. In adults there is frequently some associated spinal paralysis.

Pathology

Cranial Nerve Nuclei

The pathological changes are seen primarily in the cranial nerve nuclei and particularly their motor components. This is very similar to the distribution in the spinal cord; however, the sensory nuclei, especially those of the 8th nerve, may also be involved. Cellular inflammatory changes and nerve cell injury and destruction occur. Phagocytic activity takes place as well as vascular congestion and occasionally petechial hemorrhages.

Leptomeninges

A patchy inflammatory change is seen in the leptomeninges. The reticular formation of the medulla frequently shows severe destruction or necrotizing involvement. In the 1946 epidemic A. B. Baker and his associates found this frequently related to the hypoxia and possibly

*Presented at the Continuation Course in Neurological Emergencies sponsored by the University of Minnesota, Minneapolis, November 8, 1967.

even caused by hypoxia. In other cases it correlated well with autonomic clinical manifestations in the form of respiratory and circulatory disturbances.

Cerebral Hemispheres

The cerebral hemispheres may also be involved and occasionally produce a clinical encephalitis. The motor cortex and particularly the large motor cells are the most frequently involved. The basal nuclei of the hypothalamus may also show involvement. A cerebellar type has been described but has not been well documented pathologically.

Clinical Features

Prodromal Illness

Many cases are preceded by a prodromal illness, usually manifested by influenzal, upper respiratory or gastrointestinal infectious manifestations. There is frequently a short febrile period associated with the prodromal period. The temperature may drop to normal and then within a day or two recur, with the involvement of the central nervous system.

Neurological Involvement

The neurological involvement of the brain stem may be the first manifestation without any prodromal symptoms in a number of cases. Generally, however, there is some elevation of temperature at the time of onset.

Laboratory Findings

The spinal fluid usually shows an increased cell count at the onset. Early the cells are mainly polymorphonuclear but soon become lymphocytes or mononuclears. Twenty-five to 500 cells are common, but occasionally as many as 1,000 to 2,000 may be seen. After a week or so the cell count begins to drop and the protein content increases. The elevation of protein is usually mild to moderate but occasionally may be quite high, causing some concern about the existence of an albuminocytologic dissociation of the Guillain-Barre syndrome. Without abnormality of the cerebral spinal fluid a diagnosis of paralytic or bulbar poliomyelitis is uncertain and said to occur in only 0.5 percent of the cases.

Types of Bulbar Polio

In order to understand the various manifestations of bulbar poliomyelitis one must be familiar with the various clinical types that may occur in relatively pure form or in various combinations.

Cranial Nerve Palsy

The cranial nerve palsy group may involve either the upper or the lower cranial nerves. Marked *ocular palsies* may occur along with ptosis and various pupillary changes; or isolated ocular muscles may be paralyzed. A *Horner's syndrome* is not uncommon. There may be mild or severe paralysis of the muscles of mastication and rarely trismus caused by spasm of these muscles. The *jaw may deviate* to one side or chewing may be impossible with the mouth hanging open. Frequently the weakness can be elicited only by actual testing Some degree of *facial paralysis* occurs in about 50 percent of the cases. This is frequently unilateral but may be bilateral and may involve either predominantly the upper or lower face or the entire face. Deafness and vertigo result from involvement of the cochlear or vestibular nuclei. Vagus involvement is frequent due to involvement of the nucleus ambiguus. This causes *weakness of the palate,* pharynx and vocal cords. The palate may be flaccid or may deviate to one side. A *nasal twang* in the voice is noted. Paralysis of the pharynx causes difficulty in swallowing or inability to swallow and a pooling of secretions. Paralysis of the vocal cords causes difficulty in respiration and aspiration of secretions. Occasionally actual *laryngeal spasm* occurs. There may be inspiratory stridor. Weakness of the tongue is not uncommon and may be unilateral or bilateral and severe.

Respiratory Center

The bulbar respiratory center group may show a *variation in the depth and rate of respirations.* Later prolonged intervals between respirations develop. There is associated anxiety, restlessness, and tachycardia. Increasing periods of apnea develop. Soon there may be confusion, delirium and pulmonary congestion with ultimate cyanosis. Apnea becomes severe and hemorrhagic pneumonia is apt to occur.

Circulatory Center

The bulbar circulatory center involvement is characterized by a deep cherry-red color of the lips and a dusky-red florid, flushed appearance

of the skin. The pulse becomes very rapid, irregular and thready. The blood pressure may be elevated or low. The most consistent finding is *marked decrease in the pulse pressure*. Shock may soon follow with a falling blood pressure. The skin may become cold and clammy with a mottled cyanosis. Hyperthermia, delirium and coma are very serious signs.

Encephalitic Group

The bulbar encephalitic group is characterized by apprehension, anxiety and fear of death. The patient may become hypomanic with a flight of ideas and restlessness. *Disorientation may be prominent and insomnia may be most disturbing.* The encephalitis symptoms are difficult to differentiate from those of hypoxia. Restoration of adequate oxygenation and an adequate airway may result in an improvement or disappearance of the encephalitic symptoms, establishing their hypoxic nature. A true encephalitis involvement no doubt occurs but is rare. Involvement of the hypothalamus may result in hyperthermia, hypertension, gastric hemorrhage and severe gastric or intestinal dilatation. It should be remembered that a severe, acute dilatation of the stomach may cause elevation of the diaphragms and further embarrassment of respiration. Focal encephalitis involvement has been reported but is rare. Twitchings, myoclonic jerkings, tremors and convulsive seizures are rarely encountered. Visual verbal agnosia* has been reported. Spastic hemiparesis, unilateral ataxia, and hydrocephalus have also been reported but are poorly documented by pathological studies.

Cervical Cord Group

The bulbar cervical cord group may show any of the above types in various combinations, but in addition may show paralysis of the diaphragm, intercostal muscles and arms.

Course of Bulbar Polio

The course of bulbar poliomyelitis is frequently acute, generally reaching its peak within a period of several days to a week or so. Fever may be present for several days and drop to normal while the bulbar paralysis and involvement is still progressing.

Recovery

In the non-fatal cases improvement starts to occur generally by the second week and may continue for a rather long period. Before the advent of modern medical and respiratory therapy the mortality was extremely high. With the use of tracheotomy, intubation and artificial respiration and careful neurological and medical care the mortality has been dramatically reduced. Complete recovery has occurred in many cases, and severe residuals necessitating permanent respiratory assistance have been rare. Vital capacity has occasionally remained somewhat reduced, but often not past the point where a useful existence has resulted.

Hypoxia

Hypoxia is the most frequent and probably the most important complication of bulbar poliomyelitis. It may result in many ways. The secretions frequently obstruct the airway. The rare occurrence of trismus may make the handling of secretions difficult, and paralysis of the tongue may also contribute to obstruction of the airway. Laryngeal obstruction may result from paralysis of the vocal cords or reflex spasm of the glottis. Hypoxia may result from pulmonary edema or pneumonia. Circulatory failure may be an important causative factor. Acute gastric dilatation may cause abnormal elevation of the diaphragm, and gastric hemorrhage may lead to anemic anoxia. Hypoxia recurring from respiratory-center involvement is of very serious importance. The patient may aspirate vomitus and be unable to clear the airway because of an inability to cough. Interstitial myocarditis appears in many cases but usually disappears upon recovery.

Electrolyte Imbalance

Disturbances in water and electrolyte balance are common, especially in those receiving artificial respiration. Respiratory alkalosis or acidosis may occur. Renal infection and renal calculi also occur, as do thrombophlebitis and pressure sores.

Differential Diagnosis

This relatively common neurological disease fortunately has now become a clinical rarity, no doubt from the wide-spread use of vaccination. It still must be kept in mind, however, in any

*See Test Your Word Score Page 1213.

acute brain-stem involvement, especially when associated with fever. Differential diagnosis is generally not difficult and can usually be made without confirmatory viral studies. The latter, however, should be carried out.

Guillain-Barre Disease

The fever, the occasional prodromal symptoms, headache, leukocytosis, high sedimentation rate, meningeal signs, and spinal fluid pleocytosis easily differentiate this condition from the bulbar form of the Guillain-Barre disease.

Amyotrophic Lateral Sclerosis

Bulbar amyotrophic lateral sclerosis generally has a slower and more chronic onset and course, usually with a normal cerebral spinal fluid.

Other Diseases

Brain-stem strokes or vascular accidents generally occur in older individuals and frequently have long tract findings. Tumors of the brain stem have a slower onset and slower course and are generally associated with pyramidal tract findings. The rare bulbar form of myasthenia gravis must be differentiated; but again this condition should be associated with a normal spinal fluid examination and an absence of signs of infection. A tensilon test may be helpful, and the electromyogram may make the differential in doubtful cases. Confusion with other viral involvements of the nervous system may occur and at times may necessitate special viral studies for diagnosis. Therapy, however, is much the same. All such cases should be considered as neurological and therapeutic emergencies.

Treatment

There is no specific therapy for the virus, and immune globulin has never proven to be of any value.

Tracheotomy

Signs of airway obstruction should always be kept in mind, and early tracheotomy has been proven to be life-saving and the one main factor in altering the mortality. Probably in all cases the Ph of the blood pCO_2, the pO_2, together with measurements of ventilatory gas volumes, should be routinely performed. Artificial respiration is probably best carried out with the positive pressure respirator. Because of the short duration of the illness in some cases there is argument in favor of the nasotracheal tube. Dr. Daly felt this method could be used for as long as a period of ten days. Some anesthesiologists feel there is some danger in using it for a period longer than three or four days.

Good Nursing

Good nursing care, of course, is extremely important. Nutrition and hydration must be maintained, first by intravenous feedings and then by nasal gastric tube feedings. Scrupulous cleansing of respirators reduces the incidence of complicating pneumonia. There is no uniform agreement as to whether prophylactic antibiotics should be used.

Many problems may be encountered, taxing the ingenuity of the physician. There may be adequate oxygenation but poor elimination of carbon dioxide. Cyanosis is an unreliable guide to inadequate oxygenation. With hypoventilation oxygen may cause the patient to remain pink with a greatly reduced volume exchange. Oxygen should be used as an adjunct to, rather than a substitute or support for respiratory volume. Circulatory failure may lead to poor perfusion and resultant inadequate ventilation.

Once the patient has been started on artificial respiration constant nursing and medical supervision are necessary. Patients requiring this type of therapy are in constant danger of complications. Frequent examinations and observations are mandatory to detect and treat the resulting complications. The anesthesiologist and the internist may be very helpful consultants to the neurologist in the care of the patient seriously ill with bulbar poliomyelitis.

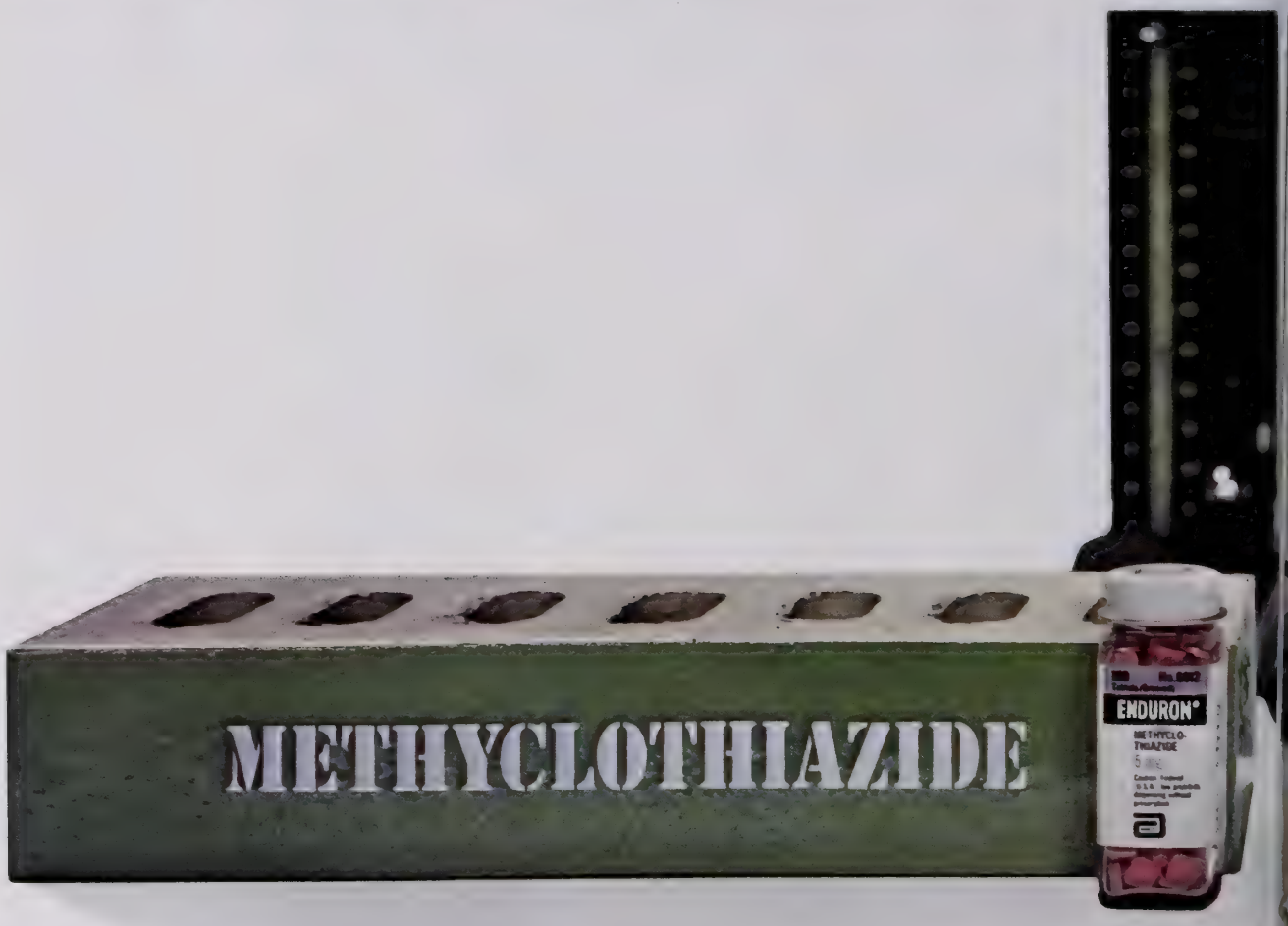
Neither man nor woman can be worth anything until they have discovered that they are fools. This is the first step toward becoming either estimable or agreeable; and until it is taken there is no hope.—Melbourne

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Use Enduron as a basic therapy in patients with mild to moderate hypertension. A single 5-mg. tablet each day is ample in most cases.

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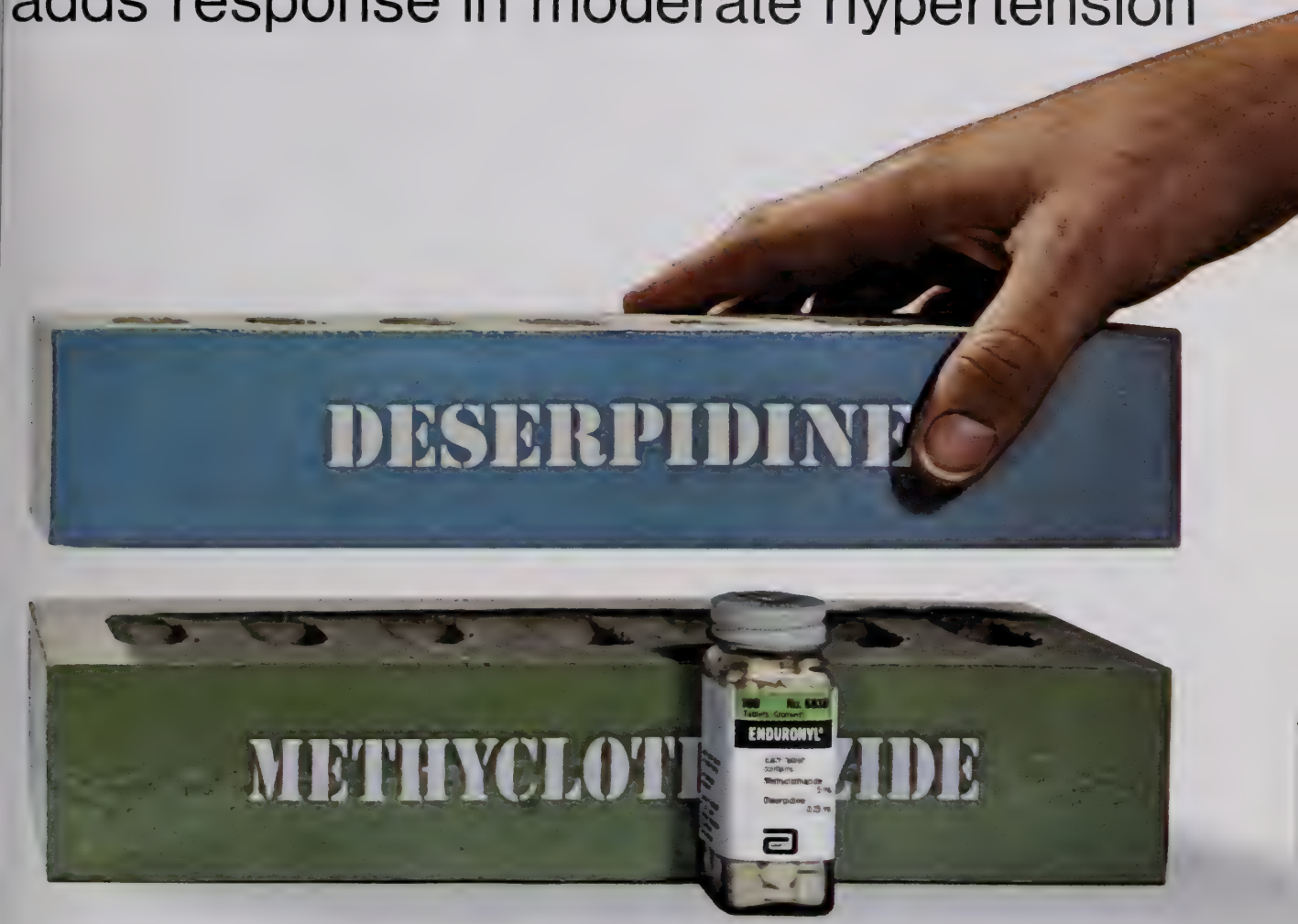
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Enduronyl is available plain or Forte. The latter provides its variation where most helpful, by doubling the deserpidine.

Use Enduronyl for patients throughout the broad range of mild to moderately severe hypertension.

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METHYCLOTHIAZIDE 5 mg. with DESERPIDINE 0.25 mg. or (FORTE) 0.5 mg.

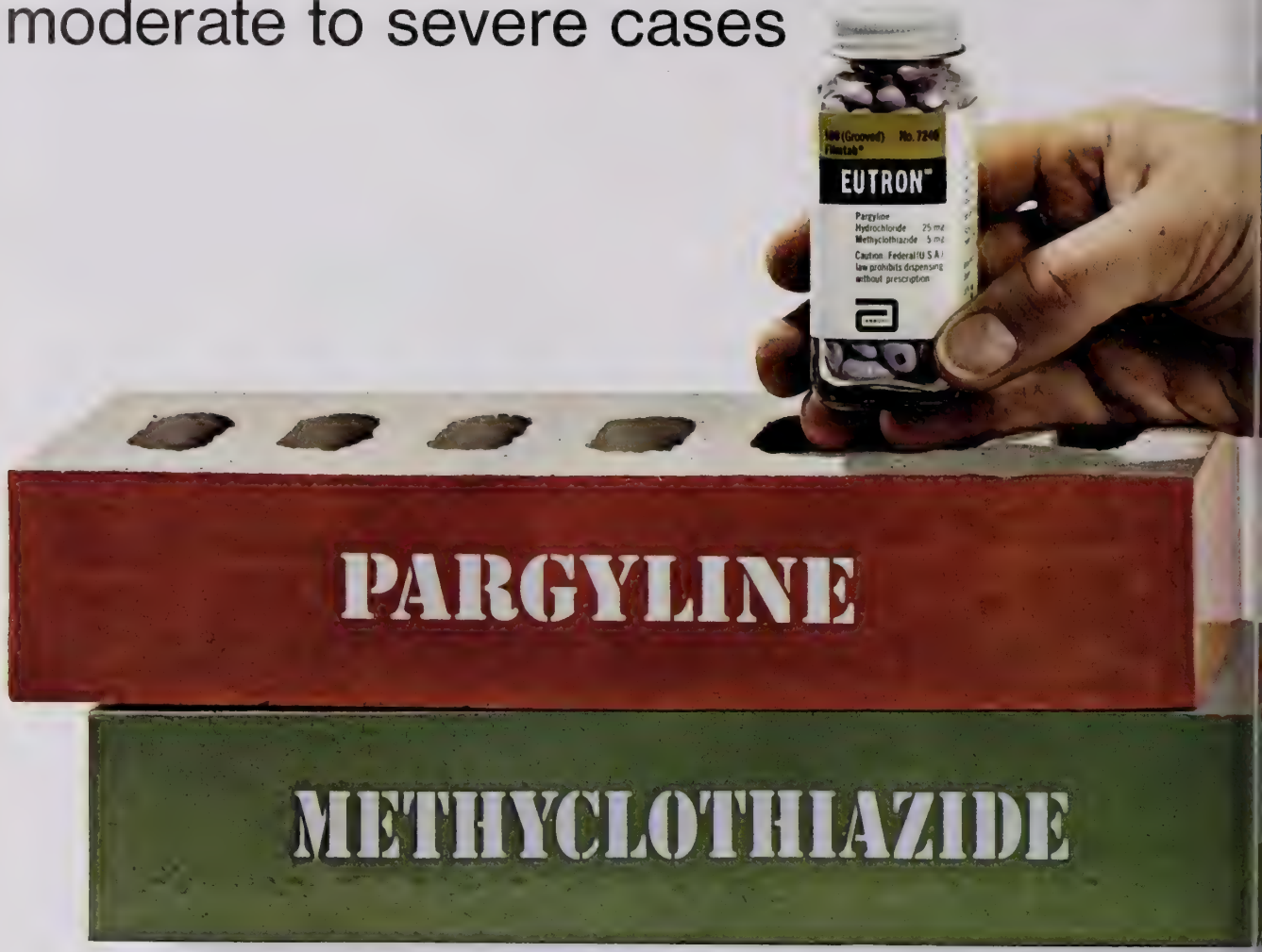
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Affords almost uniform diastolic reduction in all body positions

Eutron lowers diastolic pressures nearly equally, whether your patient is standing up or lying down.

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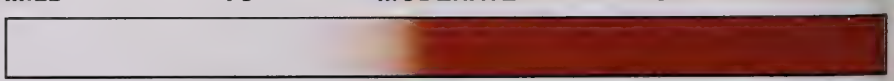
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MILD TO MODERATE TO SEVERE



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Each tablet contains
Methyclothiazide 5 mg. with
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Indications: Edema and mild to moderate hypertension (Enduron), and mild to moderately severe hypertension (Enduronyl). More potent agents, if added, can be given at reduced dosage.

Contraindications: Sensitivity to thiazides; severe renal disease (except nephrosis) or shutdown; severe hepatic disease or impending hepatic coma (hepatic coma due to hypokalemia has been reported in patients on thiazides). Do not use Enduronyl in severe mental depression, suicidal tendencies, active peptic ulcer, or ulcerative colitis.

Warnings: Consider possible sensitivity where there is history of allergy or asthma. If added potassium is indicated, dietary supplementation is recommended. Reserve enteric-coated potassium tablets for cautious use only when necessary, as they may induce serious or fatal small bowel lesions (stenosis with or without ulceration), cause obstruction, hemorrhage, and perforation often requiring surgery; discontinue them immediately if abdominal pain, distention, nausea, vomiting, or g.i. bleeding occurs. Neither Enduron nor Enduronyl contains added potassium.

Precautions: Use thiazides cautiously in severe renal dysfunction, impaired hepatic function or progressive liver disease; also in pregnancy (bone marrow depression, thrombocytopenia, and altered carbohydrate metabolism have been reported in certain newborn). In surgery, thiazides may reduce response to vasopressors, and increase response to tubocurarine. Antihypertensive response may be enhanced following sympathectomy. Watch for electrolyte imbalance (e.g., hyponatremia) in all patients. In hypokalemia (especially in digitalized patients) give supplemental potassium. In hypochloremic alkalosis, give supplemental chloride.

Use rauwolfias with caution in patients with history of peptic ulcer. Rauwolfias with anesthetics may produce hypotension and bradycardia. Discontinue Enduronyl two weeks before elective surgery. Consider vagal blocking agents during emergency surgery. In epilepsy, adjust anticonvulsant dosage. In electroshock, shorten stimulus strength and duration. In occasional patients with depressive tendencies, rauwolfias may precipitate severe mental depression that usually disappears when drug is stopped.

Adverse Reactions: Thiazide reaction include blood dyscrasias (thrombocytopenia with purpura, agranulocytosis, aplastic anemia); elevation of BUN, serum uric acid or blood sugar; anorexia, nausea, vomiting, diarrhea, headache, dizziness, paresthesia, weakness, skin rash, photosensitivity, jaundice, symtomatic gout, and pancreatitis. Cutaneous vasculitis in the elderly has been reported with other thiazides. Adverse effects with deserpidine are qualitatively similar to those with reserpine, but their incidence is lower. These include nasal stuffiness, abdominal cramps or diarrhea, nausea, headache, weight gain, reduced libido and potency, peptic ulcer aggravation, epistaxis, skin eruption, asthma in susceptible patients, electrolyte imbalance, excessive salivation, and a reversible Parkinson's syndrome. Excessive drowsiness, fatigue, weakness, and nightmares may signal mental depression. Thrombocytopenia, purpura, and a symptom manifested by dull sensorium, deafness, uveitis, glaucoma, and optic atrophy are rare allergic reactions to other rauwolfias. Hypotension from antihypertensive agents may precipitate angina attacks in susceptible individuals. Usually adverse reactions disappear when drug is withdrawn.

EUTRON™

Each tablet contains
Pargyline Hydrochloride 25 mg.
with Methyclothiazide 5 mg.

Indications—Moderate to severe hypertension.

Contraindications—Pheochromocytoma, paranoid schizophrenia, hyperthyroidism and advanced renal failure. Not recommended in malignant hypertension, children under 12, pregnant patients.

Do not use with: centrally or peripherally acting sympathomimetic drugs; foods high in tyramine (e.g., aged and natural cheeses); parenteral reserpine or guanethidine; imipramine, amitriptyline, desipramine, nortriptyline or their analogues; other monoamine oxidase inhibitors; methyldopa or dopamine; separate Eutron and these agents by two weeks.

Sensitivity to thiazides; severe renal disease (except nephrosis) or shutdown; severe hepatic disease; impending hepatic coma from thiazide-induced hypokalemia.

Warnings—Patients: 1. No other drugs (particularly "cold preparations" and antihistamines), cheese or alcohol without physician's consent. 2. Promptly report orthostatic symptoms, severe headache, other unusual symptoms. 3. Angina pectoris or coronary artery disease patients must not increase physical activity with improved anginal symptoms or well-being.

Physicians: 1. Use antihistamines, hypnotics, sedatives, tranquilizers and narcotics (meperidine contraindicated) cautiously in reduced doses. 2. Stop Eutron two or more weeks before elective surgery; in emergency surgery reduce premedication (narcotics, sedatives, analgesics, etc.) to 1/4 to 1/5; carefully adjust anesthetic dosage to patient response. 3. Use cautiously in advanced renal failure. 4. Pargyline may induce hypoglycemia. 5. Consider possible sensitivity reactions when a history of allergy or asthma is present. 6. If potassium is indicated, dietary supplement is recommended; enteric-coated potassium tablets may induce serious or fatal small bowel lesions (stenosis with or without ulceration), cause obstruction, hemorrhage, and perforation frequently requiring surgery; discontinue medication immediately if abdominal pain, distention, nausea, vomiting or gastrointestinal bleeding occurs; Eutron does not contain added potassium. 7. Possible systemic lupus erythematosus has been reported for thiazides.

Precautions—Pargyline: Use cautiously at reduced dosage: caffeine, alcohol, antihistamines, barbiturates, chloral hydrate, other hypnotics, sedatives, tranquilizers, narcotics. Periodically do urinalyses, blood counts, liver function tests, etc. Use with caution in liver disease. Watch for orthostatic hypotension, especially in impaired circulation (e.g., angina pectoris, coronary artery disease, cerebral arteriosclerosis); also, augmented hypotension in concomitant febrile illnesses. Reduce or discontinue if hypotension is severe. In impaired renal function watch for cumulative drug effects, elevated BUN and other evidence of progressive renal failure; withdraw drug if these persist. In surgery increased central depressant response (hypotension and increased sedative effect) can be controlled by (1) discontinuing at least two weeks prior; (2) in emergency surgery lowering dose of premedication; (3) when necessary, administering a vasopressor. Do not use in hyperactive and hyperexcitable patients. Pargyline may unmask severe psychotic symptoms where emotional problems pre-exist. Use cautiously in Parkinsonism, especially with antiparkinsonian agents. In prolonged therapy, examine for change in color perception, visual fields, fundi and visual acuity. Also, prolonged therapy has made certain patients refractory to nerve blocking effects of local anesthetics.

Methyclothiazide: Use cautiously in severe renal dysfunction, impaired hepatic function or progressive liver disease; also in pregnancy (bone marrow depression, thrombocytopenia, and altered carbohydrate metabolism have been reported in certain newborn). In surgery thiazide may reduce vasopressor response and increase tubocurarine response. Antihypertensive response may be enhanced following sympathectomy. Watch for electrolyte imbalance (e.g., hyponatremia). Give supplemental chloride if hypochloremic alkalosis occurs and supplemental potassium if hypokalemia occurs (especially in digitalized patients). Thiazides may decrease serum P.B.I. without signs of thyroid disturbance.

Adverse Reactions — Pargyline: Orthostatic hypotension and associated symptoms, mild constipation, fluid retention, edema, dry mouth, sweating, increased appetite, arthralgia, nausea, vomiting, headache, insomnia, difficult in micturition, nightmares, impotence, delayed ejaculation, rash, purpura, weight gain, hyperexcitability, increased neuromuscular activity and other extrapyramidal symptoms. Drug fever is extremely rare. Reduction in blood sugar and hypoglycemic effects are possible. Congestive heart failure has been reported in a few patients with reduced cardiac reserve.

Methyclothiazide: Blood dyscrasias (thrombocytopenia with purpura, agranulocytosis, aplastic anemia); elevation of BUN, blood sugar or serum uric acid (gout may be induced); anorexia, nausea, vomiting, diarrhea, headache, dizziness, paresthesia, weakness, skin rash, photosensitivity, jaundice and pancreatitis. Cutaneous vasculitis in elderly patients has been reported with other thiazides.

If side effects are severe or persist, reduce dosage or withdraw drug. 804438R

ABBOTT

TM-TRADEMARK

Clinical Reviews

A program of lectures and discussions on problems of general interest in medicine and surgery will be presented at the Mayo Clinic and Mayo Foundation, Rochester, Minnesota. Identical sessions are offered on October 28, 29 and 30 and November 11, 12 and 13.

This program is acceptable for credit by the American Academy of General Practice and the College of General Practice of Canada. The registration fee for this program is $20.

The number of physicians who can be accommodated is necessarily limited. For this reason identical programs will be offered two successive weeks. The program will be presented first on October 28, 29 and 30 and repeated on November 11, 12 and 13. Those wishing to attend should communicate with M. G. Brataas, Mayo Clinic, Rochester, Minnesota 55901, indicating which session they would prefer to attend.

A Program of Clinical Experience in Outpatient Education for Control of Diabetes Mellitus

The Diabetes Detection and Education Center, 916 East 15th Street, Minneapolis, Minnesota, has developed a program of medical and paramedical education for physicians, nurses, public health personnel, and dietitians. The course includes five days of intensive instruction in the medical, nursing and dietetic team approach to management of diabetes mellitus in the outpatient. The purpose of the course is to develop maximum skills in medical and paramedical personnel so that patients may receive optimum care, and physicians may be relieved of time consuming, intensive instruction of the patient with diabetes. Classes are scheduled for the weeks of: July 22, August 5, August 26, September 9, September 23, October 7, October 28, November 4, November 18, December 2, December 16, and December 30. Rooms and meals are available at the Center at minimum cost.

For further information, contact D. D. Etzwiler, M.D., or C. B. Cohen, M.D., at the above address.

National "Outstanding Service" Award Given Minnesota Physicians Planning Service Corporation Organization

The Minnesota office of Physicians Planning Service Corporation, a Nationwide medical service organization, has been named that organization's "outstanding service office in 1967."

The award to James J. Krakowski, CLU, and his associates, 406 Pioneer Building, St. Paul, was made at a recent meeting in New York on behalf of the 50,000 physicians who are serviced by PPSC.

Presenting an inscribed clock to Mr. Krakowski to commemorate the honor were Dr. Edward R. Annis, a past president of the American Medical Association, and Dr. Edwin Dunlop, director of research at the Fuller Sanitarium, South Attleboro, Mass. Both Drs. Annis and Dunlop are trustees of the National Association of Residents and Interns and the American Professional Practice Association. NARI, APPA and the Phi Delta Epsilon fraternity are medical organizations for whose members Physicians Planning Service Corp administer a wide range of socio-economic benefits. The award received by Krakowski was the top service citation for agencies serving these members of the medical profession.

Optic Neuritis*

JAMES A. MORIARTY, M.D.†
Minneapolis, Minnesota

OPTIC NEURITIS may be classified as to location of the lesion in the optic nerve. Those neuritic lesions involving the optic nerve which are visible upon funduscopic examination are described by Walsh as intraocular. Lesions posterior to the eye are retrobulbar; those peripheral to the optic nerve are perineuritic.

Retrobulbar neuritis is a term which usually indicates involvement of the papillomacular bundle of the optic nerve in its orbital or intracranial course. Ronne included any level of the optic nerve from the orbit to the lateral geniculate body.

The involvement of the optic nerve in optic neuritis is the result of inflammation, demyelinization or degeneration.[1]

Symptoms and Signs

The intraocular optic neuritis, often called papillitis, has a sudden onset with marked visual loss and is usually unilateral. *There is associated eye pain, pain with movement of the eye, and headache.*

Children with optic neuritis experience spontaneous pain in the involved eye, pain on movement of the eye, and tenderness to palpation, as adults do. Children have a headache more frequently than adults; however, there is a greater tendency to simultaneous bilateral involvement and greater frequency of papillitis than retrobulbar neuritis.[13]

The funduscopic examination is primarily one of congestion, infiltration, exudation. The veins are dilated and the arteries narrowed. Elevation of the disc is limited, the margins are blurred and there may be hemorrhages. Exudate occurs over the disc and the retina. Twenty-three percent of Carroll's[2] patients complained of head pain, usually on the same side as the optic neuritis and located above and behind the eye. More frequently than not the pain developed before the visual loss—usually

*Presented at the Continuation Course in Neurological Emergencies sponsored by the University of Minnesota, Minneapolis, November 8, 1967.

†Assistant Professor, Division of Neurology, University of Minnesota Hospitals.

a day or two preceding, but sometimes even two to four weeks before visual impairment. Tenderness to palpation of the globe occurred in 16 percent.

Optic Neuritis vs. Papilledema

Ophthalmoscopically optic neuritis cannot be differentiated from papilledema on a single examination. Papilledema usually has constriction of the peripheral fields. The peripheral field of optic neuritis is generally unrestricted to a large test object. Whereas the blind spot is enlarged in papilledema, optic neuritis has a central field defect; color vision defect often persists and concentric constriction of the central isotopes is present.

Papilledema can most readily be identified when one or more of the following changes have intensified: hyperemia of the disc, blurred disc margin, venous engorgement with loss of pulsation, loss of physiological cupping, and protrusion of the disc. Frequent and repeated funduscopic examination reveals progression in these features of papilledema, whereas none of these alone is sufficient to diagnose papilledema.

Etiology

In Adults

One third of Carroll's series of 240 cases of optic neuritis had demyelinating disease diagnosed as multiple sclerosis. One third had spontaneous occurrence of the optic neuritis and one third, a variety of associated diseases, including diseases of the adjacent structures, infectious diseases, non-infectious conditions, toxic agents, Leber's hereditary disorder, and vascular disease.

An unusual toxic etiology[3] of optic neuritis caused by the monoamine oxidaze inhibitor pheniprazine (Catron) caused three similar cases. The patients used pheniprazine for one month. There was marked impairment in the color vision. Later the visual acuity was moderately lowered. In most cases full recovery is seen after withdrawal of the drug.

Cataract extraction may result in optic neuritis.[4]

In Children

No cause could be determined in 53% of the 41 patients studied by Kennedy and Carroll.[13] Half of the children with undetermined cause of the optic neuritis had some infection immediately preceding or concomitantly with the attack of optic neuritis. Usually the infection was an upper respiratory tract infection.

Twenty-seven percent of the children had optic neuritis associated with familial or generalized disease. These conditions included diabetes, malnutrition, measles, congenital syphilis and a hereditary disorder called Leber's disease.

About 20% of the children with optic neuritis had associated multiple sclerosis in a mean follow-up time of eight years.[14]

Diagnosis

With a diagnosis of expected retrobulbar neuritis, investigation includes a complete neurological examination, lumbar puncture, skull x-rays, electroencephalogram, a brain scan using technetium 99m and, when indicated, contrast studies including cerebral angiography and/or pneumoencephalography.

Differential Diagnosis

The differential diagnosis of optic neuritis includes a wide range of treatable and untreatable conditions. The arteritis and mass lesions which produce optic neuritis lend themselves to therapeutic benefit after the diagnosis has been made. Treatment may be of benefit in the hereditary degenerative types of involvement.

Mass Lesion

There is a real danger of mistaking an intracranial process for retrobulbar neuritis. Central defects of the visual field may arise. Chamlin found no normal peripheral fields in 33 cases of intracranial mass lesions with central scotoma.

In ruling out intracranial tumors which can present with scotomata, the neurological examination may show focal signs and symptoms

TABLE I

Proportion of Patients in Treated and Control Groups with Normal Vision on Entry and at Days 1, 8, 15, 22, and 30.

Day of trial	Proportion (%) with Normal Vision	
	Corticotrophin	Control
1	4%	8%
8	56%	12%
15	76%	20%
22	80%	30%
30	92%	52%

and signs of progressive involvement. The skull x-ray is viewed for erosion of the sella, the sinuses or the sphenoid ridge. A cerebral spinal fluid protein may be elevated. Slow wave or spike abnormality on the electroencephalogram may be helpful in detecting a neoplasm.[5]

Ninety-five percent of the meningiomas scanned using technetium 99m gave positive results.[6] Small tumors near the chiasm and dorsum sella were the only ones likely to be missed on brain scan technique.

The chiasmal lesion gives rise to a clockwise progressive field defect in the left eye and a counter-clockwise progressing field defect in the right eye. Both begin with a superior temporal field defect.

Ischemic Optic Neuritis

Ischemic optic neuritis results in acute visual failure, as does optic neuritis from other causes. Pallor results with or without edema. Retinal vessels may be attenuated. There is a minimum of funduscopic findings.

The basic lesion is a *progressive occlusive process affecting the ophthalmic artery* in its branches to the optic nerve, retina, and extra ocular muscles. Thrombosis is not a constant histological feature in ischemic optic neuritis when giant cell arteritis is seen. It is likely that intimal proliferation is the main cause of reduction in size of the arterial lumen, resulting in ischemia of the optic nerve.[7] Blindness probably results from failure of the circulation in the optic nerve due to extensive involvement of the short and posterior ciliary arteries around the optic nerve head. Ischemic optic neuritis or infarction of the optic nerve is probably the commonest cause of visual loss in giant cell arteritis, although central retinal artery occlusion has been demonstrated ophthalmoscopically and histologically. MacFaul recommends a consideration of *giant cell arteritis* in the differential diagnosis of optic nerve ischemia in elderly people.

The differential features of ischemic optic neuropathy and optic neuritis were outlined by C. J. Earl[8] (Table 2).

Temporal Arteritis

In 1962 Simonds and Cogan designated a syndrome called temporal arteritis, the classical symptoms of which are absent or present only after the ocular phase of the disease. The patient may have only a history of vague headaches, general malaise, loss of weight and anorexia. Tenderness and swelling of the temporal artery may be absent or minimal.

The disorder presents as a quiet ischemic blindness in one eye, followed by a similar occurrence in the second eye after an interval of days or weeks.

Temporal artery biopsy may be positive despite the absence of classical symptoms in this region. The erythrocyte sedimentation rate may be increased.

A common cause of blindness in the elderly is occult temporal arteritis.

Of the 46 patients studied by Cullen[9] with the typical picture of central retinal artery occlusion, six were proven to have temporal arteritis by temporal artery biopsy. The typical picture consisted of arterial spasm, or obliteration with edema of the retina and a cherry-red spot.

Of the 20 patients with ischemic optic neuritis, 11 were proven to have temporal arteritis by temporal artery biopsy. These cases showed an acute visual failure, usually complete or nearly so, inactive or sluggish pupils, more often than not pale edematous disc or pallor without edema, a few hemorrhages on the disc, and retinal vessel attenuation.[9]

TABLE 2

	Ischemic Optic Neuropathy	vs.	Optic Neuritis
Onset	A more sudden onset		A less sudden onset
Pain	Pain on movement of eye is uncommon		Pain upon movement of eye is common
Disc appearance	Swollen but grey disc		Hyperemic and swollen
Appearance of veins	Retinal arterioles narrowed		No narrowing
Visual loss	Complete blindness in one or both eyes in 30% of cases		Central or paracentral scotoma

All patients with ischemic optic neuritis should be presumed to be suffering from occult temporal arteritis until proven otherwise. Cullen found that 50% of his patients with ischemic optic neuritis had temporal arteritis, and that 10% with a central retinal artery occlusion had temporal arteritis.

The treatment of occult temporal arteritis is 40 units of ACTH I.M. b.i.d. pending confirmation of the biopsy, followed in a few days by prednisone, 40 mg. P.O. daily, with reduction of the dosage as the blood sedimentation rate begins to decrease after seven to 10 days of therapy.

Hereditary Optic Atrophy (Leber's disease)

Leber's disease is a relatively acute central visual loss involving both eyes. The clinical picture is one of bilateral retrobulbar neuritis. Onset is from age 15 to 25 years. It occurs usually in males and has sex-linked or recessive hereditary features. Considerable visual impairment is to be expected.

Neuromyelitis Optica (Devick's disease)

Devick's disease is a necrotizing degenerative process which involves both optic nerves with optic neuritis and the spinal cord with a transverse myelitis. Either the optic neuritis or the transverse myelitis may precede the other. There is complete tissue necrosis in the areas involved and cavity formation results. Cerebral symptoms of headache, changes in consciousness, and convulsions occasionally occur. The patient may have either one attack with remission or repeated episodes. Paraplegia and severe visual impairment result.

Pseudo-Papilledema

Pseudo-papilledema is to be differentiated from optic neuritis. Pseudo-papilledema may occur with hyperoptic or astigmatic refractive errors and with Drusen deposits in the disc head. Pseudo-papilledema is sometmies seen congenitally.

Prognosis of Optic Neuritis

The overall prognosis is dependent upon the etiological factor, response to therapy where indicated, the possible development of disseminated sclerosis, and age.

Prognosis in Relationship to Age

The prognosis for vision was better for those patients less than 45 years of age. Average time of recovery of maximal visual acuity was two months, irrespective of age and sex. The fastest recoveries occurred in a sixteen-year-old girl whose vision improved from 6/60 to 6/6 within two weeks, and in a 23-year-old whose vision improved from 6/18 to 6/6 in a similar length of time. Two patients, however, took six months to return to normal vision.

A good recovery was defined as one in which the final corrected visual acuity was 6/9 or better. In the younger age group, less than 45 years of age, three out of 83 (4%) failed to make a good recovery. In the older age group five out of 21 (24%) made little or no recovery. The reason for this difference is unknown, although a relatively poor blood supply in the older patients may be responsible for the poor recovery as well as the increased frequency of a more severe visual acuity loss initially at the onset of the optic neuritis.[12]

Optic Neuritis in Children

The natural course of optic neuritis in children is one of spontaneous recovery. Improvement begins before the end of the third week and reaches a maximum of visual improvement by six months.[13]

Relationship of Retrobulbar Neuritis to Multiple Sclerosis

In evaluating 87 individuals with retrobulbar neuritis over an interval of 10 to 15 years 32% developed disseminated sclerosis.[10] In the younger age group, between 20 and 44, 50% had a chance of developing disseminated sclerosis.[10]

In a mean follow-up time of eight years children who had optic neuritis were less prone to develop multiple sclerosis than the young adult. Eight of 33 children did develop multiple sclerosis.[13]

Visual Field Studies and Optic Nerve Involvement

In the remission phase of multiple sclerosis, depression of the visual field is the most common tangent screen (2 meter) finding. Central or paracentral scotomata plus depression of the visual field is the next most common finding. Central or paracentral scotomata without depression of the visual field was not found in 123 patients in the remission phase.[11]

Thus visual field studies gave a much better indication of the involvement of the optic nerves than the ophthalmoscopic examination. Although one third of Zeller's patients experienced a visual loss at the onset, 74% had visual field changes at some stage of the disease.[11] Detection of the visual field deficit was facilitated by decreasing the level of illumination from seven-foot to four-foot candles.[11]

Treatment

Patients treated with corticotrophin improved more rapidly than the control group who had retrobulbar neuritis in one eye and were not treated. At the end of 30 days of treatment a much higher proportion of the treated group had regained normal vision (using Jaeger scale J1-J2). Forty units of corticotrophin were given daily intramuscularly.

This advantage to the treated group becomes evident at the end of the first week but is most distinct at the end of two weeks.[14]

Rawson noted the rapid relief of eye pain in the corticotrophin-treated group, all of whom experienced relief within a few hours of the first injection and became free of pain within 48 hours. The control group on the other hand often continued to have orbital pain for a period of two weeks. When the visual acuity was lower than the 16 level, the corticotrophin group clearly improved faster.

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Shakespeare: Pharmacologia
Mandragora

"Give me to drink mandragora,
That I might sleep out this great gap of time
My Antony is away."*

Thus does Cleopatra address her attendant Charmain, when separated from her lover, Antony.

Mandragora, a soporific and narcotic prominent and popular in medieval European pharmacology, is likewise referred to in "Othello" when the villain Iago says of Othello:

"Not poppy, nor mandragora,
Nor all the dreamy syrups of the world,
Shall ever medicine thee to that sweet sleep,
Which thou ow'dst yesterday."†

Mandragora was a derivative from the mandrake plant, an herb similar to the May apple and one of the potato family.

*Antony and Cleopatra I,5.
†Othello III,3.

SOUTHERN MINNESOTA MEDICAL ASSOCIATION CONVENTION PROGRAM

September 20, 1968—Owatonna, Minnesota

The Maximal Care Unit—The Responsibility of the Small Community Hospital. *Dr. M. A. Keil, Albert Lea*

The Use of the Barron Food Pump in Surgical Patients with Nutritional Problems. *Dr. D. P. Anderson & Dr. W. J. O'Rourke, Austin*

Circulatory Collapse after Thorazine in Bronchial Asthma.
Dr. James Tiede & Dr. G. H. Peters, Rochester

Hyperinsulinism—Advances in Diagnosis and Management—Review of 154 Cases. *Dr. D. A. Scholz, Rochester*

"When to do What" in Pediatric Surgery. *Dr. Bernard Spencer, Minneapolis*

PANEL—The Pill—Uses and Abuses. *Dr. E. Hammes—Moderator, Minneapolis*

1. What Pill for which patient?
   Dr. D. Decker, Rochester
2. Thrombosis and the Pill, fact or fantasy.
   Dr. F. Kazmier, Rochester
3. Ancillary therapeutic effects of the Pill.
   Dr. Mel Sinykin, Minneapolis

Synovianalysis: Importance in Differential Diagnosis of Rheumatic Diseases.
Drs. Tompkins & Ward, Rochester

Congenital Body Banding—Case Report with 44-year Follow Up.
Dr. Jerry Hanson, Rochester

Urologic Problems in Children:

1. Recurrent urinary tract infections.
   Dr. E. Burke, Rochester
2. Obstructive uropathy.
   Dr. P. Kelalis, Rochester

Revascularization of the Heart. *Dr. W. R. Schmidt, Minneapolis*

Confusing Masses in the Groin—Diagnostic and Therapeutic Implications.
Dr. Karl A. Lofgren, Rochester

Applications of the Doppler Principle to Diagnosis.
Dr. F. M. Owens, Jr., St. Paul

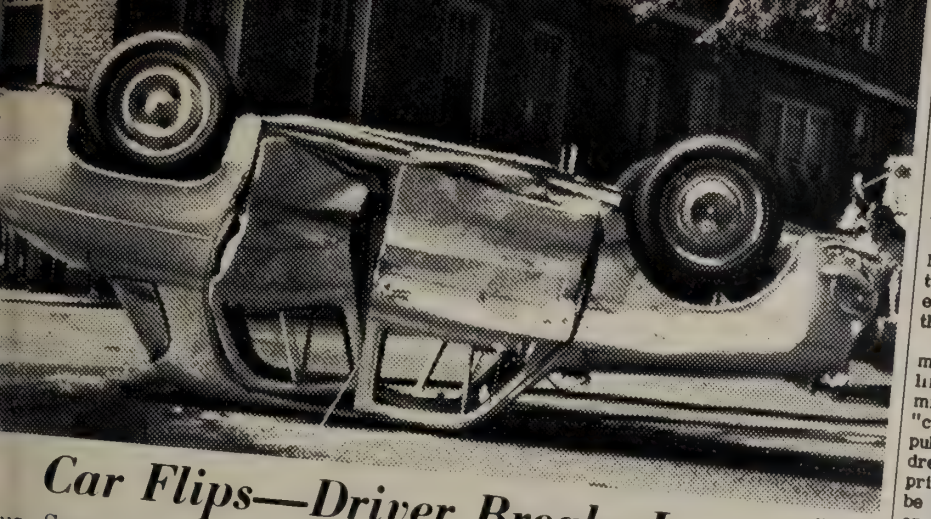
Malignant Melanomas of the Head and Neck. *Dr. John N. Simons, Rochester*

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In this Program the U.S.A. physician sends direct to a fellow specialist overseas his specialty journal(s); we supply the name and address of the overseas doctor and the subject of the journal desired. From then on it is a liaison strictly between the two—one in the U.S.A. and the other "somewhere overseas."

If you wish to participate, please send the titles of journals (particularly specialty journals) you will mail to colleagues overseas to: Ada Chree Reid, M.D., Director, AMA DOCTOR TO DOCTOR PROGRAM, 10 Columbus Circle-Room 1270, New York, New York 10019.



STAFF PHOTO

Car Flips—Driver Breaks Leg

us, Sept. 7. John P. Jones of
ar incurred a broken leg today
driving

Patrolman B. R. Brown, the car hit a fire hydrant and flipped over on its top
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He's had enough excitement for one day.

For the patient who has been through an accident, the worry and anxiety following the experience may actually heighten the perception of pain. This is why there's a classic ¼ grain *sedative* dose of phenobarbital in Phenaphen with Codeine—*to take the nervous "edge" off,* so the rest of the formula can control the pain more effectively.

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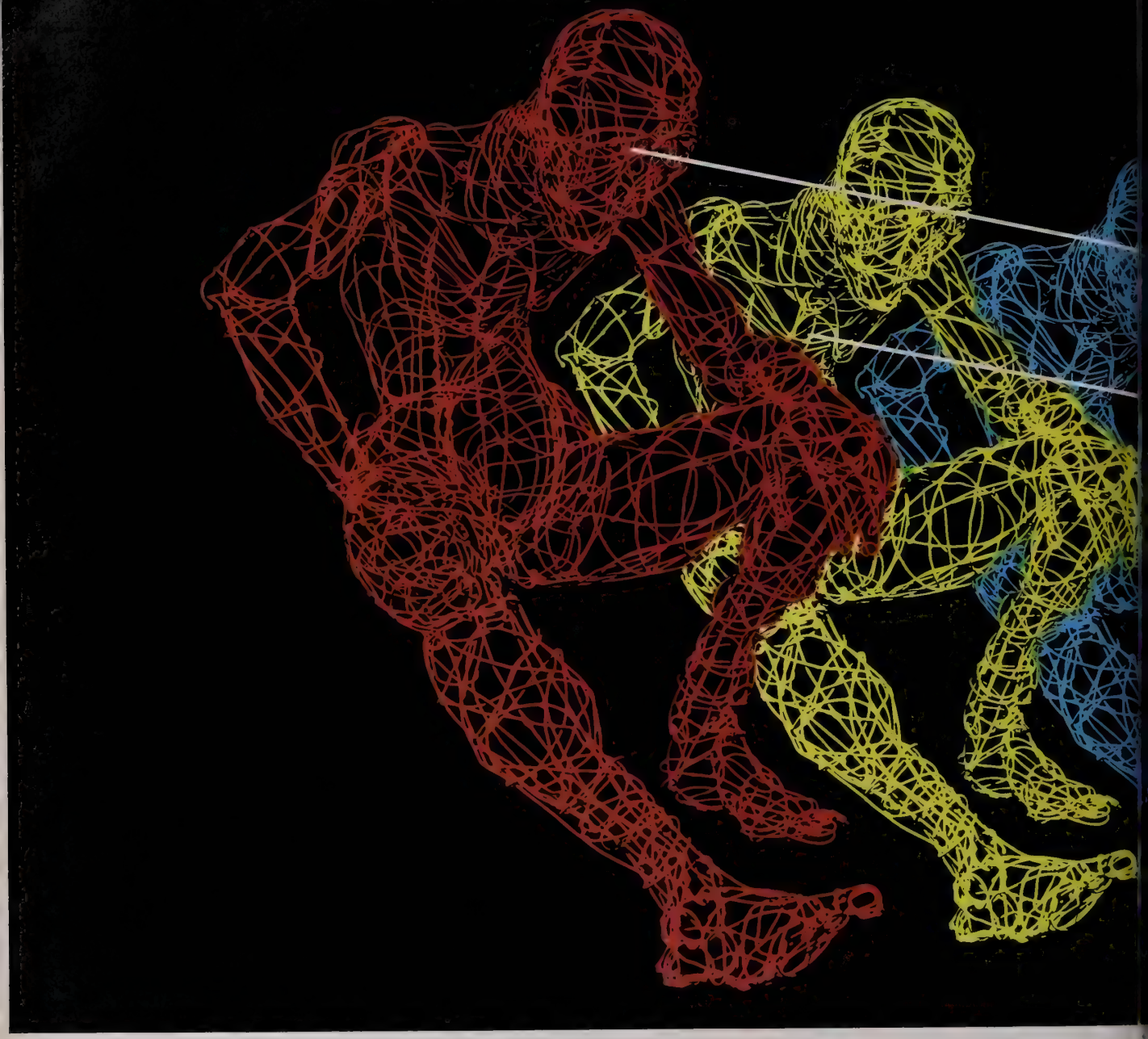
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Iron, Elemental (as Ferrous Fumarate)	110 mg.
Ascorbic Acid (Vitamin C)	75 mg.
Folic Acid	1 mg.

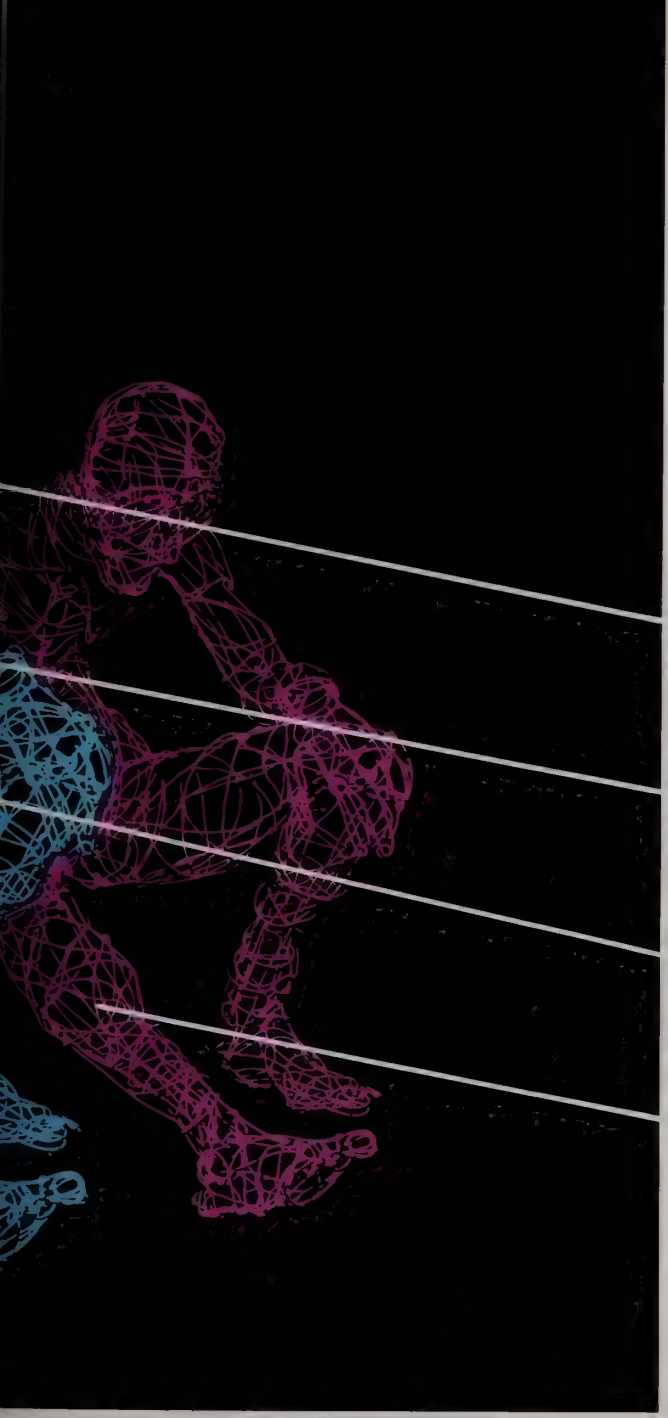
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Composition: Each Mylanta chewable tablet or teaspoonful (5 ml.) contains: magnesium hydroxide, 200 mg.; aluminum hydroxide, dried gel, 200 mg.; simethicone, 20 mg. *Dosage:* One or two tablets (well chewed or allowed to dissolve in the mouth) or one or two teaspoonfuls to be taken between meals and at bedtime.

Stuart

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ATLAS CHEMICAL INDUSTRIES, INC.

Acute Poisoning*

EDWARD JIMENEZ-PABON, M.D., PH.D.†
Minneapolis, Minnesota

DRUGS OR CHEMICALS become harmful to man if they accumulate rapidly and in abnormal amounts within the body tissues. This state of acute intoxication may develop following accidental, suicidal or criminal exposure to these compounds.

Accidental poisoning may occur at any age, although it is more common in the first five years of life[1] when children frequently put many objects into their mouth. In adults, accidental poisoning results from attempts at self-medication or mistaking one drug for another.

Suicidal poisoning is most common in the late teens and early twenties.[2]

Criminal poisoning is not frequent and presents less of a problem than the preceding two types of intoxication.

Acute intoxication can follow exposure to so many drugs or chemicals that only the most common ones will be discussed. These include the barbiturates, salicylates and tranquilizers. Poisoning is also produced, not uncommonly, by carbon monoxide, organophosphorus compounds, heavy metals, chlorinated hydrocarbons, ethanol and methanol. All of these compounds are capable of producing stupor, convulsions, coma and death.

The human body is capable of detoxifying and eliminating poisons. However, when the amount of the intoxicant exceeds the capacity of the body to terminate its activity, complications and death may ensue unless therapy is initiated promptly. Therefore, therapy in acute intoxication should include: (1) prompt identification of the poison; (2) removal of the unabsorbed poison from the body as soon and as completely as possible; (3) maintenance of cardiopulmonary functions; (4) elimination of all absorbed poisons as rapidly as

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*Presented at the Continuation Course in Neurological Emergencies sponsored by the University of Minnesota, Minneapolis, November 8, 1967.

†Neurology Service, Veterans Administration Hospital and University of Minnesota, College of Medical Sciences, Minneapolis.

possible, and (5) use of antidotes whenever feasible.

Identification of the Poison

If the patient is conscious he may be able to identify the poison as well as the amount and the time he took it. However, if he is unconscious, his clinical state and laboratory findings may prove to be the only way of identifying the intoxicant. Table 1[4,5,22] summarizes some clinical and laboratory findings in common cases of intoxication. The clinical findings observed in meprobamate and glutethimide poisoning are similar to those seen in barbiturate intoxication. Up until last year only five fatal cases of ingestion of chlorpromazine had been reported, all of them involving

TABLE 1

Important Clinical and Laboratory Findings in Common Cases of Poisoning

Drug or chemical	Clinical findings	Laboratory findings
1. barbiturates	hypoventilation patchy erythema or blisters coma	spectral analysis to identify and distinguish individual barbiturates. blood levels of about 1 mg/100 ml may be considered lethal for rapid acting barbiturates. blood levels greater than 5 mg/ml may be lethal in long-acting barbiturates.
2. salicylic acids	hyperventilation sweating hyperthermia	blood levels $>$ 30 mg/100 ml should be considered toxic. ferric chloride diacetic acid urine test positive. hypoprothrombinemia.
3. tranquilizers: phenothiazine	hypoventilation hypotension convulsion, coma extrapyramidal reaction	ferric chloride test positive in urine.
4 carbon monoxide	bright red color of the fingernails; cherry-pink lips; smell of utility gas on clothes; hypoventilation	blood: carboxyhemoglobin 60-80%; in elders, 30% or more carboxyhemoglobin may be significant.
5. organo-phosphorous compounds	pinpoint pupils cold sweating salivation muscular twitching convulsions; coma	85% or more of the red cell cholinesterase may be inhibited before there are any overt indications of poisoning.
6. lead	lead line in gingival margin; seizures disorientation auditory or visual hallucinations	stippled red blood cells coproporphyrinuria. lead excretion in urine more than 0.15 mg/l.
7. nonbarbiturate sedatives glutethimide (Doriden)	hypoventilation coma laryngopharyngeal musculature laxity	blood levels 1 mg or more may indicate poisoning.
8. methyl alcohol	hyperventilation blurry vision seizures delirium	at death, blood levels as low as 0.05% or even less may be significant.
9. cyanide	pink skin color odor of bitter almonds hypoventilation hypotension	fatal blood levels about 1 mg/100 ml.
10. morphine	pinpoint pupils greatly depressed respiration coma	morphine found in the urine and feces.

children.[3] Drug intoxication with chlordiazepoxide and diazepam have not been fatal. Although deep stupor and coma develop, little fall in blood pressure or respiratory depression has been noticed with these last two drugs.[3]

Removal of the Unabsorbed Poison

Whenever possible, an intoxicant should be removed from the stomach,[6] particularly if less than four hours have elapsed since its ingestion.[7] Many drugs that have been in the stomach for much longer periods of time can be removed in considerable amounts. For instance, since many major tranquilizers delay gastrointestinal motility and are water soluble, substantial amounts can be successfully removed hours after their ingestion.[3]

Emesis

Emesis can be induced if the patient has not vomited by the time he is seen. Emetics such as syrup of ipecac, apomorphine, dilute solutions of copper sulfate and potassium antimony tartrate are available.[7] The latter two are highly toxic and therefore not recommended. Syrup of ipecac in doses of 4-8 ml can be given by mouth. It acts as a local irritant to the stomach and also stimulates the chemoreceptor trigger zone in the floor of the fourth ventricle. Emesis is not prompt, there being a long latency period of about thirty minutes to an hour or more before its effects are felt. Apomorphine, however, is fast and dependable. Vomiting usually occurs five to 10 minutes after a single subcutaneous dose of 5 mgm in adults and 1 mgm in children. The use of emetics is not recommended if poisoning has occurred with corrosives or if the patient is comatose. Many authors do not encourage the use of emetics.[8] They do not believe these drugs are completely effective; and there is always the danger of an aspiration pneumonia. Gastric aspiration and lavage using copious amounts of water are preferred. In the unconscious patient aspiration or lavage, if done, should follow intubation or tracheotomy. The Scandinavian method of treating acute barbiturate intoxication does not recommend gastric lavage because of its low yield and the dangers of aspiration pneumonia.[9]

Absorbents

Powdered activated charcoal can be introduced into the stomach.[7] Poisons that exist in simple aqueous solutions may be absorbed readily by the charcoal. Some of them include mercuric chloride, sulfanilamide, nicotine, barbiturates, salicylic acid, alcohol, parathion and phosphorus. A saline cathartic is often given to accelerate the passage of the charcoal through the gastrointestinal tract.

Cardiopulmonary Systems

The Airway

The respiratory airway should be cleared from all secretions since over-secretion in the bronchial tree frequently occurs. Failure to do so may result in pulmonary atelectasis and pulmonary infections: the most common clinical complications of drug intoxication.[9] Tracheal intubation becomes necessary if the larynx cannot be kept clear of secretions. Intubation should not be prolonged over 36-48 hours; otherwise, it may produce a tracheolaryngitis or eventually a vocal cord granuloma.[10] Tracheotomy becomes mandatory if (1) secretions continue to be troublesome after intubation, (2) the patient has been comatose for more than 48 hours, or (3) there is no cough reflex present. Mechanical respiration is needed only when respiration begins to fail.

Ventilation

Abnormal ventilation can give rise to disturbances in the acid-base balance. The hyperventilation seen in salicylate poisoning is due to a direct effect of this drug on the brainstem respiratory center.[11] Hyperventilation decreases the partial pressure of carbon dioxide within the alveoli and arterial blood. This is followed by a rise in blood pH which, if not limited by the compensatory mechanisms of the body, will progress to a respiratory alkalosis. No specific treatment is needed to correct the respiratory alkalosis.

In barbiturate poisoning hypoventilation is secondary to hypoxemia and an accumulation of carbon dioxide.[12] Respiratory acidosis with a lowered blood pH develops as a consequence of the resulting hypercapnia. The hypoxemia, in turn, is responsible for the metabolic acidosis. Both types of acidosis will aggravate the existing hypoventilation. Therapy consists of ventilation using supernormally large ventilation volumes. Arterial CO_2 and O_2 as well as the pH should be determined in order to follow

the progress of treatment. Measurements of oxygen tension must also be made.

Pulmonary Edema

Pulmonary edema may develop as a result of a decrease in the osmotic pressure of the blood, an increase in the permeability of the pulmonary capillaries or, more likely, a distention of the capillaries of the lungs as seen in left ventricular failure.[13] Treatment would include use of oxygen, forced diuresis with osmotic diuretics if the kidneys are functioning adequately, defoaming therapy with inhalation of oxygen using a high concentration of alcohol vapor, and digitalization if needed.[13] If the patient is in a state of shock, plasma expanders such as macrodex or blood should be administered. Pressor amines are also used to maintain blood pressure.

Excretion of All Absorbed Poisons

There are many ways in which poisons can be eliminated from the body once they are absorbed. By inducing pulmonary hyperventilation, carbon monoxide and many volatile solvents such as methyl alcohol, xylene, methyl bromide, and trichloroethylene can be eliminated through the respiratory system.[9] At present there are no known ways of stimulating the biliary excretory mechanism in order to promote the elimination of poisons through the gastrointestinal tract.[7] Renal excretion of intoxicants is encouraged by the use of forced diuresis and diuretics and by altering the urinary pH.

Forced Diuresis

Forced diuresis with urea was first used in Denmark. In the U.S.A. mannitol and chlorothiazide have also been used extensively. In forced diuresis by a water load, the excess water inhibits the secretion of antidiuretic hormone by the posterior pituitary. The main effect of this excessive amount of water will be on volume and flow in the distal renal tubules and in the collecting ducts. Since foreign neutral compounds and many organic acids and bases are reabsorbed to a great extent at the proximal tubules, the water load will not increase appreciably the excretion of these substances.[7] Addition of an *osmotic diuretic* which exerts its action at the proximal tubules will decrease water reabsorption, thereby increasing the excretion of the passive solute. If urea is used, serum levels should be kept below 400-500 mg/ml. Since urea can diffuse through the proximal renal tubule, mannitol, which is a hexahydric alcohol and therefore impermeable to most cell membranes, has been preferred to urea as an osmotic diuretic.[11] In salicylate poisoning, an intravenous priming dose of 500 ml of 25% mannitol can be given in the first 30 minutes, to be followed by one liter of the solution every two hours for a total of twelve liters in 24 hours. If the urine flow has not reached 6 ml per minute after four hours, the infusion may have to be stopped. If the flow is less than 1 ml per minute, fluids should be stopped and dialysis should be considered.[14]

Diuresis can be further increased by *manipulating the urinary pH.* Many drugs and poisons are pH-dependent for excretion. Weak

TABLE 2

Hemodialyzable Drugs and Chemicals

A. *Sedatives*
1. barbiturates
2. Glutethimide (Doriden)
3. ethynylcyclohexylcarbamate (Valmid)

B. *Tranquilizers and antidepressants*
1. imipramine (Tofranil)
2. amitryptyline (Elavil)
3. meprobamate (Equanil)
4. ethclorvynol (Placidyl)
5. phenelzine (Nardil)
6. chlordiazepoxide (Librium)
7. pargyline hydrochloride (Eutonyl)

C. *Anticonvulsives*
1. diphenylhydantoin (Dilantin)
2. primidone (Mysoline)

D. *Analgesics*
1. salicylic acid
2. methyl salicylate
3. dextro propoxyphene hydrochloride (Darvon)
4. acetophenetidin (Phenacetin)

E. *Halides*
1. bromide
2. radio-iodide

F. *Alcohols*
1. methanol
2. ethanol
3. ethylene glycol

G. *Metals*
1. calcium
2. BAL—mercury complex
3. lead
4. arsenic
5. sodium
6. potassium

H. *Antibiotics*
1. streptomycin
2. kanamycin
3. penicillin
4. sulfamethoxypyridazone (Kynex)
5. sulfisoxazole
6. tetracycline
7. chloramphenicol
8. nitrofurantoin (Furadantin)
9. isoniazid

I. *Miscellaneous*
1. aniline
2. dextroamphetamine
3. thiocyanate
4. carbon tetrachloride

acids tend to be excreted more rapidly if the urine is alkaline, and weak bases will be excreted faster if the urine is acid. Only the undissociated portion of a weak acid or base will diffuse freely across the tubule cells.[14] In salicylate poisoning free salicylate excretion is dependent on the urinary pH. In an alkaline urine up to 85% of free salicylate will be eliminated, while only a low of 10% of the dose will be excreted in an acid urine.[11] Alkalinization can be accomplished by the use of sodium bicarbonate, an inhibitor of carbonic anhydrase activity like Diamox, or by an organic buffer such as THAM. In adults, infusion of 0.9% saline, 5% dextrose and 2% sodium bicarbonate given in rotation at an initial rate of about two liters per hour will produce a diuresis in excess of 5 ml per minute at a urine pH of about 7.5.[11] The use of carbonic anhydrase may lead to acidosis with resulting convulsions and papilledema.

Forced diuresis has also been used successfully in meprobamate, glutethimide and bromide poisoning.[15]

Dialysis

Hemodialysis and intermittent peritoneal dialysis are the preferred methods of dialysis and are more effective than forced diuresis.[16] Schreiner[17] states that hemodialysis is most effective if:

(a) the poison molecule can diffuse through cellophane from plasma water and has a reasonable removal rate or dialysance;

(b) the poison is well distributed in accessible body fluid compartments and not bound to protein molecules. Since the major tranquilizers are strongly bound to plasma proteins, dialysis would probably be ineffective;

(c) a relationship exists between toxicity and the blood concentration and duration of the body to exposure of this circulatory poison. Anticholinesterases do not meet this requirement. Their rapid action prevents a relationship between blood levels and clinical toxicity to be established;

(d) the amount of poison dialyzed constitutes a significant addition to the normal body mechanism for dealing with the poison.

Hemodialysis and peritoneal dialysis are the only possible ways of treating patients with grossly impaired renal function and intoxication with long-acting barbiturates eliminated through the kidney only. Hemodialysis is the method of choice in methyl alcohol intoxication and other cases of poisoning where tissue damage can occur very quickly.[15,16] Table 2 lists many drugs and chemicals that are hemodializable.[16]

If facilities for hemodialysis are not available, intermittent peritoneal dialysis using 5% albumen on the dialyzing fluid combined with alkalinization of the urine can be used. This method is less expensive, less complicated and easier to control than hemodialysis. In spite of this, pediatricians have found it more practical and certainly less complicated to use exchange transfusion in children in cases of severe poisoning.[6,11,16]

Antidotes

Antidotes can counteract the activity of a poison. Unfortunately, there are few specific antidotes available. These are listed in Table 3.[2,4,18-23]

The *chelating agents* seen in Table 3 are substances capable of forming stable covalent complexes with polyvalent metal ions. These complexes are frequently not toxic.

The *narcotic antagonists* overcome the respiratory depression caused by morphine and its derivatives. Respiration improves within minutes toward normal and consciousness may return promptly.

Specific Poisons

Organophosphorus

The organophosphorus compounds have been used in the treatment of myasthenia gravis. Their use as insecticides has been increasing steadily. They are capable of combining with acetylcholinesterase, forming a phosphorylated acetylcholinesterase compound which is unable to hydrolyze acetylcholine.[19] Accumulation of acetylcholine at the motor end plates of striated muscles and cholinergic nerve endings gives rise to weakness and paralysis of striated muscles, overactivity of the parasympathetic system, central nervous system excitation, as-

TABLE 3

Some Antidotes Used in Acute Poisoning

Antidotes	Acute poisoning by	Doses
A. Chelating agents		
1. Dimercaprol (BAL)	arsenic*	Initial injection is usually 5 mg/Kg by intramuscular injection; followed by 2.5 mg/Kg in 2 to 3 hours and a third injection of 2.5 mg/Kg 2 to 3 hours later. In the second 12-hour period, two more injections of 2.5 mg/Kg are given. Thereafter, two doses per day for 2 or more days.
2. BAL-glucoside (more soluble)	mercury* gold	
3. Calcium disodium versenate; versene	lead*	1.0 to 2.0 gm per day, best given in two infusions at 12-hour intervals in 5-day course with 2 days rest between
4. N-penicillamine	copper*	1-4 gm daily by mouth
5. D-acetyl-D, L-penicillamine (less toxic than #4, above)	lead iron mercury	
6. Desferrioxamine (D.F.M.)	iron*	5-10 gm D.F.M. in water given by stomach tube to neutralize iron in gut. Intravenous infusion of D.F.M. 90 mg/Kg body weight in 100 ml of 5% aqueous dextrose solution given over a period of 1-2 hours.
B. Narcotic antagonists		
1. Nalorphine	morphine and its derivatives	5-10 mg intravenously or 0.1 mg/Kg intravenously in children.
2. Levallorphan		1-2 mg intravenously or 0.02 mg/Kg intravenously in children.
C. Oximes		
1. 2-pyridine aldoxime methyl-chloride (2-PAM chloride, Pralidoxime chloride)	organo-phosphorous compounds	*adults:* 1 gm 2-PAM chloride intravenously at a rate not to exceed 500 mg/minute, or this amount diluted with 250 ml of sodium chloride injection and infused over a 30-minute period. A dose of 1 gm may be repeated in one hour if necessary. *children:* 20-40 mg/Kg of body weight or 0.6-1 gram/square meter of body surface of 2-PAM chloride at a 5% solution given intravenously.
D. Atropine sulfate	organo-phosphorous compounds	*adults:* 2-4 mg atropine intravenously and repeated at 5-10-minute intervals until signs of atropine toxicity appear. Some degree of atropinization should be maintained for at least 48 hours. *children:* 0.5-1 mg intramuscularly or intravenously every 10-15-minute intervals until signs of atropine toxicity appear.
	muscarine carbachol neostigmine and other quaternary ammonium compounds	0.25-2 mg atropine sulfate intramuscularly.
E. Oxygen		
1. hyperbaric oxygen 2. oxygen and 5% carbon dioxide	carbon monoxide	place patient in a pressure chamber at 2-2.5 atmospheres until levels of carboxyhemoglobin reach zero or until the patient becomes conscious.
F. Nitrites		
1. amyl nitrite 2. sodium nitrate	cyanide	inhale amyl nitrite 0.3 ml.
G. Sodium thiosulfate	cyanide	50% solution given intravenously.

*Opposite antidotes are best agents against poisoning with these metals.

phyxia and death. There is no correlation between cholinesterase depression in the blood and clinical signs and symptoms. Pralidoxime chloride should be given as soon as possible together with intravenous injections of atropine. Little is accomplished if the oxime is administered more than 36 hours after exposure to the organophosphorus poison has occurred, since phosphorylated acetylcholinesterase ages quickly, converting itself into a non-reactivable form.[19,20]

Carbon Monoxide

Oxygen is used under pressure in carbon monoxide poisoning in an effort to saturate the alveoli and blood with this gas, thus accelerating the displacement of carbon monoxide in carboxyhemoglobin. Treatment with 100% oxygen at 2 atmospheres of pressure will return consciousness within 30-90 minutes.

Cyanides

Cyanides combine with cytochrome oxidase which is an enzyme needed in cellular respiration. Methhemoglobin, produced in the blood by the administration of nitrites, competes with cytochrome oxidase for cyanide and, in so doing, aids in the regeneration of the enzyme.[4] Sodium thiosulfate is also given in cyanide poisoning. It acts by promoting the conversion of cyanide to harmless thiocyanate.[4]

Analeptic* treatment is not recommended following poisoning with depressants, as many investigators believe they are ineffective in severe poisoning.[8,12] The patient response to these drugs is transient, and there is always danger of inducing cardiac arrythmias, convulsions, visual hallucinations and psychoses.

Summary

Common drugs or chemicals producing acute poisoning include the barbiturates, salicylates and tranquilizers.

Therapy of acute intoxication includes prompt identification of the poison and its removal from the stomach by the use of emetics, gastric aspiration and lavage. The respiratory airway should be kept clear of secretions, and normal ventilation should be maintained. If necessary, blood pressure can be supported by using plasma expanders, blood or pressor amines. Renal excretion of intoxicants is encouraged by the use of forced diuresis with the aid of diuretics and by altering the urinary pH. Dialysis can also be used and is more effective than forced diuresis in removing poisons from the body. Whenever possible, antidotes should be used to counteract the activity of the intoxicant.

Finally, the use of analeptics is to be discouraged. They are thought to be inefficient in severe poisoning and capable of producing severe side effects.

*See Test Your Word Score Page 1213.

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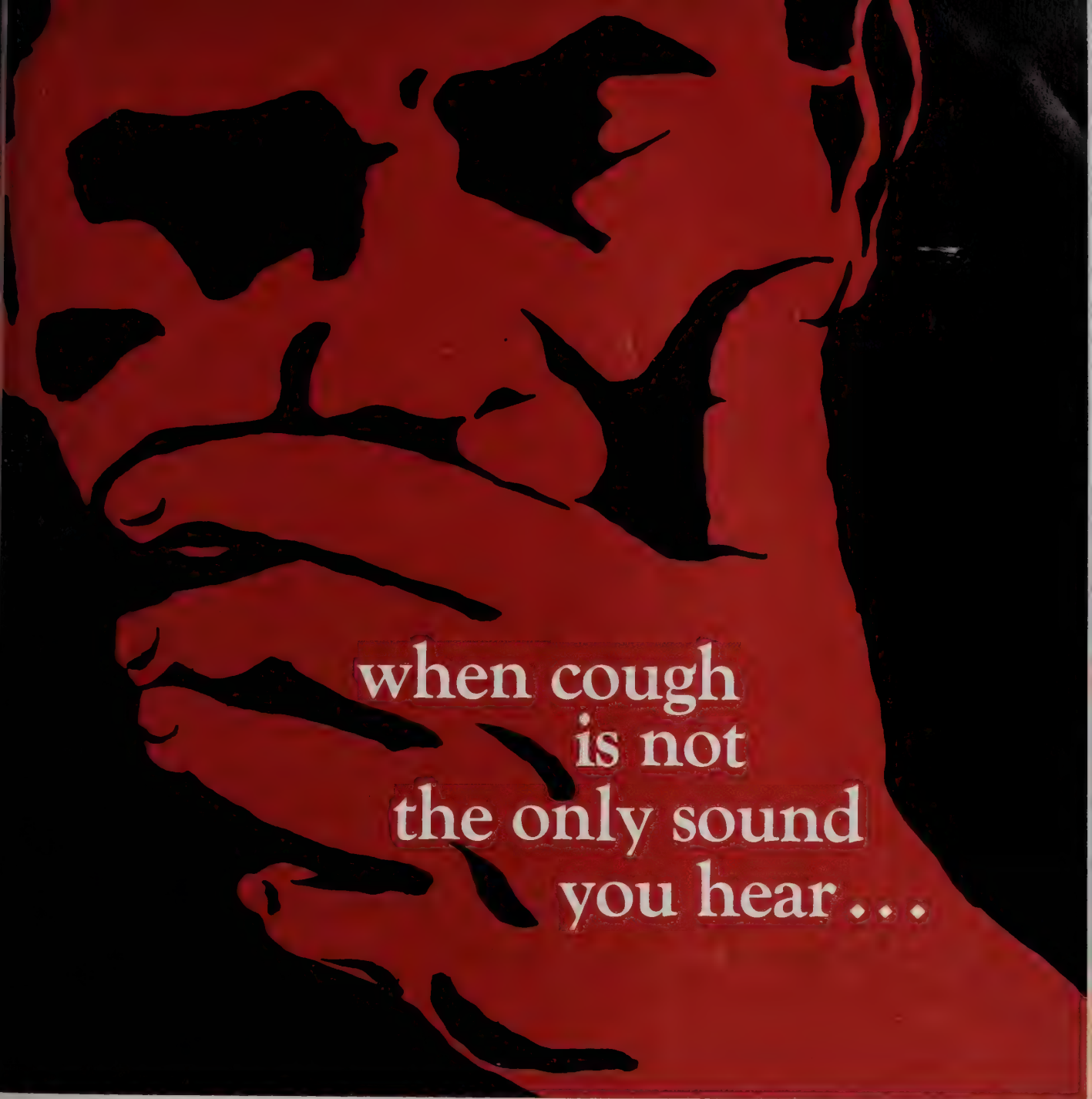
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Adverse Reactions: *Central Nervous System*—Drowsiness, especially with large doses, early in treatment; infrequently, pseudoparkinsonism and other extrapyramidal symptoms; nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache. *Autonomic Nervous System*—Dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, nasal stuffiness, and pallor. *Endocrine System*—Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema. *Skin*—Dermatitis and skin eruptions of the urticarial type, photosensitivity. *Cardiovascular System*—Changes in the terminal portion of the electrocardiogram have been observed in some patients receiving the phenothiazine tranquilizers, including Mellaril (thioridazine hydrochloride). While there is no evidence at present that these changes are in any way precursors of any significant disturbance of cardiac rhythm, several sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients previously showing electrocardiographic changes. The use of periodic electrocardiograms has been proposed but would appear to be of questionable value as a predictive device. *Other*—A single case described as parotid swelling.

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WILLIAM J. RILEY, M.D., Ph.D.†
Minneapolis, Minnesota

INTERNAL CAROTID insufficiency can be defined as a symptomatic perfusional deficit in the neural field supplied by the artery of the same name. The clinical presentation of this disease depends on the circumstances peripheral to the internal carotid artery. Variations in the circle of Willis can greatly alter the neural field irrigated by the internal carotid artery, and pre-existing lesions in this neural field can greatly change the expression of a perfusional deficit.

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Etiology

Of the many potential causes of internal carotid insufficiency including the several types of vasculitis, osteoarthritis, local tumor, trauma, and arterial fibromuscular dysplasia, only atherosclerosis will be discussed. In our culture this is the most prevalent cause of internal carotid insufficiency. Accompanying this process are changes such as lumenal narrowing, intimal ulceration, and elongation causing tortuosity and kinking. Each of these changes may produce reduction of blood flow in some

*Presented at the Continuation Course in Neurological Emergencies sponsored by the University of Minnesota, Minneapolis, November 8, 1967.

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individuals and thereby contribute to the cerebral symptomatology of this disease.

Pathogenesis

With elongation and tortuosity of the internal carotid artery the redundancy of the vessel may allow it to become kinked at a site of connective tissue fixation or become otherwise so mechanically trapped as to reduce its lumen and the flow of blood to the neural field it irrigates. Clinical symptoms in this situation are often precipitated by movement of the neck or by constricting clothing.

With progressive reduction of the lumen of the vessel by an atherosclerotic plaque, usually just above the common carotid bifurcation, the field of irrigation becomes increasingly dependent on collateral or substitutive vessels. When finally the collateral channels cannot supply the metabolic needs of the neural field there is the onset of intermittent, progressive, or permanent symptoms of internal carotid insufficiency.

If there is disruption of the integrity of the intima of the internal carotid artery, as from an ulcerated atherosclerotic plaque, the possibilities of embolism threaten the perfused field. Emboli may be small like the microemboli of cholesterol crystals, fibrin, or platelet aggregates, or large as with fragmentation of or seeding from a thrombus on the plaque. The symptoms of disease may be intermittent, progressive, or permanent.

Symptoms and Findings

A characteristic and initial sign of internal carotid insufficiency is sudden transient monocular blindness with sensory and/or motor deficit on the side contralateral to the involved vessel. The latter is usually more pronounced in the face and hand than in the leg. If the major hemisphere is involved, aphasia may be an additional feature.

This clinical presentation derives from the usual cerebrovascular pattern in which the ophthalmic artery is the first major intracranial branch from the internal carotid artery; and the middle cerebral artery field of irrigation is largely dependent on the internal carotid artery, with a relatively disadvantaged relationship to potential collateral supply.

*See Test Your Word Score Page 1213.

Transitory Neurologic Dysfunction

From this classic picture there are many variations. Some of the previously mentioned features may appear without the complete ensemble. An unusual mode of presentation is progressive dementia with quadriparesis; but such an unusual presentation requires consideration of possible complicating features or other predisposing causes. Symptoms may include headache, mental changes, transient loss of consciousness, visual disturbances, seizures, disorientation, drowsiness, and emotional lability. It is said that more than 40% of patients with carotid artery insufficiency have warning symptoms of transitory neurologic dysfunction prior to the onset of a permanent deficit.

Localizing Findings

On examination the patient may have a wealth of localizing findings during a clinical attack or may have no abnormalities on detailed investigation between attacks. Aside from the localizing value of a motor or sensory deficit, suggestive findings include a significant bruit over the carotid bifurcation, reduction of pulsations either over the carotid artery palpated in the neck, or over the internal carotid artery palpated in the oral pharynx. Other findings may include: (1) an ipsilateral* Horner's syndrome due to damage to the cervical sympathetics in the carotid sheath, (2) an ocular bruit over the ipsilateral eye, or (3) an ipsilateral optic atrophy due to pressure on the optic nerve from an enlarged ophthalmic artery (flowing retrograde as a collateral for the insufficient internal carotid artery).

Bedside Studies

Useful bedside investigations include ophthalmo-dynamometry, the determination of pressure in the central retinal artery, the arm-to-retina fluorescein circulation time, and thermography or the more simple measurement of temperature over the medial half of the forehead bilaterally. This area is perfused by the ophthalmic artery and can therefore be an indicator of internal carotid flow. Carotid compression tests at the bedside are potentially hazardous and should not be done without electroencephalographic and electrocardiographic monitoring.

Diagnostic Aids

In the patient who has sustained cerebral infarction in consequence of internal carotid insufficiency the electroencephalogram or brain scan may be of diagnostic aid. A series of either of these and especially a series of both may help to separate a case of internal carotid insufficiency with cerebral infarction from a cerebral tumor. Usually the routine laboratory work, chest and skull x-rays, echoencephalogram, and lumbar puncture are of little value. A special modification of the encephalogram test is occasionally of great value in diagnosing or screening. To conduct this test the patient is given 0.6-1 mg. of atropine I.M. one-half hour prior to the test to block vasovagal cardiac slowing. He is then connected for encephalogram recording with one channel recording an electrocardiogram trace. Each of the carotid arteries in the neck is then massaged to test for adequacy of atropinization as well as for extreme cerebral dependence on flow through that carotid. If no changes such as clinical symptoms, electrocardiogram slowing or encephalogram abnormalities are produced, each carotid artery is compressed in turn for 30 seconds or until changes are noted. The emergence of clinical symptoms or localized encephalogram abnormality in the absence of slowing of the heart rate is regarded as presumptive evidence that the responsible area of cerebrum has a critical dependence on the compressed carotid artery. The finding of symptoms emanating from the hemisphere contralateral to the compressed carotid artery or the appearance of an encephalogram abnormality in the contralateral hemisphere, along with absence of similar findings from compression of the ipsilateral carotid artery, suggest insufficiency or complete occlusion of the carotid artery ipsilateral to the changes.

A definitive diagnosis rests on clinical suspicion plus adequate arteriographic study. Usually an adequate study requires visualization of at least three and usually all four cervicocranial vessels either by aortography or by direct puncture angiography.

Therapy and Prognosis

Already alluded to have been the different time courses with which symptoms of this entity may present: transient and recurring, progressive, or permanent. Consideration of the time course is a major deciding factor for both treatment and prognosis. For the patient with findings that may be due to internal carotid insufficiency the time course cannot be predicted. Will the findings remain stable? Will they progress? Will they relent? It is this very uncertainty that makes the patient a potential medical emergency.

Those patients with stable neurologic deficit with or without a history of antecedent transient attacks or a subacute onset prior to being seen represent cases of completed stroke syndrome. Their care need not differ from that given other patients with completed stroke.

Anticoagulation

For those patients with a relatively mild deficit and progressive disability over a period of observation urgent attention is required; if possible the progress of the stroke must be halted and hopefully reversed. After intracerebral and subarachnoid hemorrhage have been excluded by a clear lumbar puncture, and when the diagnosis is reasonably certain, immediate anticoagulation with heparin followed later by a coumadin derivative is required in the absence of severe hypertension, bleeding tendency, or other contraindication to anticoagulants. Other measures, such as intravenous papaverine, low molecular weight dextran, and intermittent inhalation of 5 per cent CO_2, are still under study. After anticoagulants are begun and the patient has stabilized, consideration can be given to elective arteriography to demonstrate the causative lesion. When any doubt exists as to the diagnosis, anticoagulation may be deferred until after a definitive diagnosis is established by arteriography.

Arteriography

It is particularly important to exclude such diagnoses as cerebral tumor, and subdural or epidural hematoma which may occasionally appear as a progressing stroke. For this reason arteriography often precedes anticoagulation.

In the unequivocal case of the patient with internal carotid insufficiency already anticoagulated and now being investigated by elective arteriography, it will be necessary to study the majority of the cervico-cranial vessels before

deciding on surgical correction of the lesion. Because such an investigation is extensive and has a distinct morbidity and mortality rate, it should not be undertaken unless adequate vascular surgery facilities are available. Since this investigation is time-consuming and has the potential of further impairing the already marginal blood supply, many prefer to have the patient already receiving the benefits of prophylactic anticoagulation before the investigation is undertaken.

Transient Ischemia

Some patients present with no findings of neurologic deficit but a history of transient ischemic attacks. They may have other findings compatible with a diagnosis of internal carotid insufficiency such as a cervical bruit. Other patients may be seen for the first time during an attack of insufficiency but are observed to clear completely in a brief time. In these patients an elective evaluation can be undertaken with emphasis on safety and completeness. If, in such patients as these, the diagnosis of internal carotid insufficiency be sustained, a decision regarding therapy can be made. Before this decision is made, however, the hazards to the patient from the induced hemorrhagic diasthesis should be weighed against the frequency and severity of the transient ischemic attacks he has had. In treating with anticoagulants the patients suffering from transient attacks of cerebral ischemia, the only benefit established is a reduction in the number and severity of the attacks. There is as yet no demonstrated protection from an eventual stroke. This limited benefit must be weighed against the hazards of anticoagulation and special attention given to any existing "relative" contra-indications.

Surgical

When localized, surgically accessible, extracranial occlusive vascular disease is found, it should be corrected by a competent vascular surgeon. In cases where the vascular occlusive process is too scattered, where there is extensive intracranial vascular disease which appears more significant than that in the neck, or where the patient refuses surgery, consideration can be given to long-term treatment with anticoagulants.

Conclusions

By internal carotid insufficiency we mean that circumstance in which the symptoms and signs of neurologic deficit suggest that their cause is an inadequate perfusion through either or both of the internal carotid arteries.

Patients whose disease is due to this pathogenetic mechanism and who show progressive neurologic deficit represent medical emergencies. The keystone to successful management of patients with a progressing stroke due to internal carotid insufficiency is recognition of the evolving pattern of neurologic deficit and appreciation of the need for immediate diagnostic and therapeutic measures. This recognition depends on careful observation of the patient for evolution of symptoms or signs suggesting progressive deficit. Such a patient needs immediate institution of measures to support and increase the flagging local cerebral circulation. These measures include, but may not be restricted to, immediate anticoagulation and the surgical correction of the appropriate vascular obstruction. Diagnostic studies must advance rapidly so as not to delay appropriate therapy.

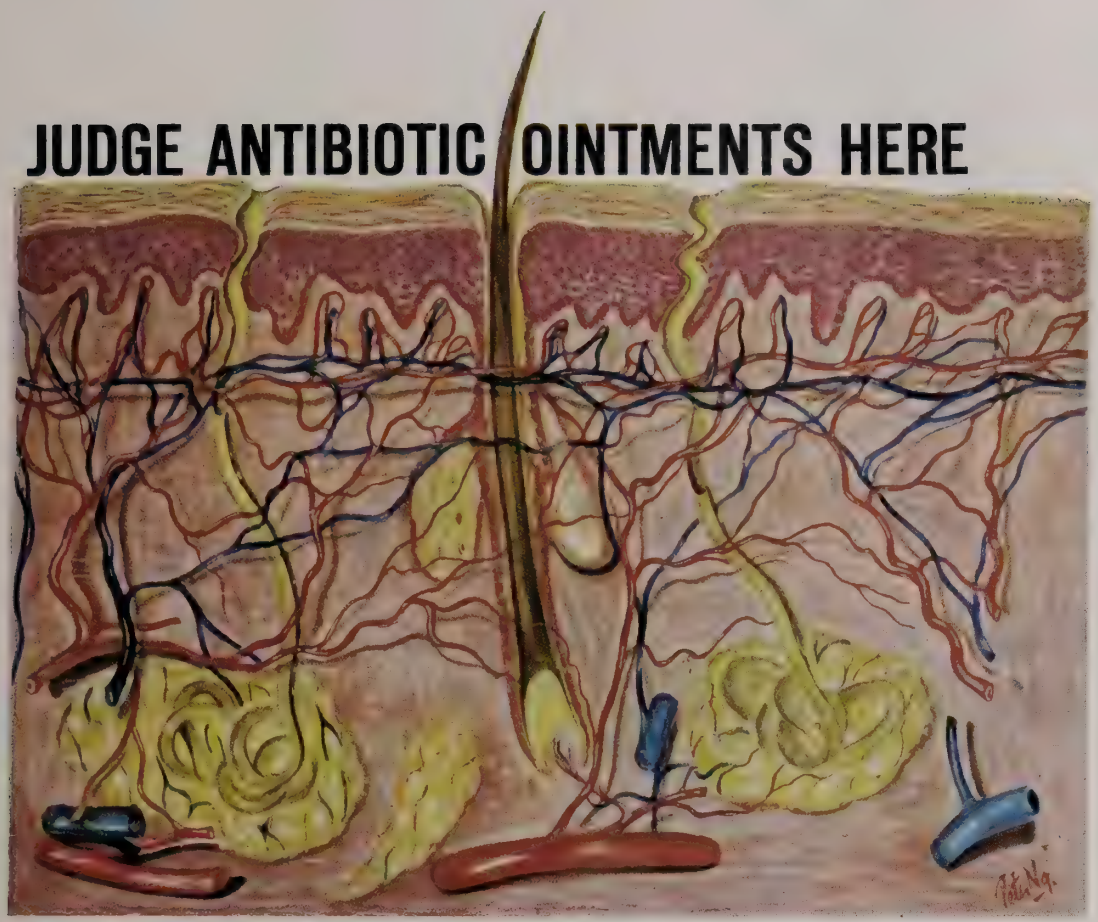
The patient with transient attacks of cerebral ischemia due to internal carotid insufficiency also requires careful appraisal and management; but the workup of his problem is an elective one. The patient with stable neurologic deficit due to internal carotid insufficiency presents no emergent problem and requires only the usual careful attention to supportive general medical management and rehabilitative care.

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4-7 May be secured from the author or the reprints.

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Precautions: Before prescribing, carefully select patients, avoiding those responsive to routine measures as well as contraindicated patients. Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patient should not exceed recommended dosage, should be closely supervised and should be warned to discontinue the drug and report immediately if fever, sore throat, or mouth lesions (symptoms of blood dyscrasia); sudden weight gain (water retention); skin reactions; black or tarry stools or other evidence of intestinal hemorrhage occur. Make complete blood counts at weekly intervals during early therapy and at 2-week intervals thereafter. Discontinue the drug immediately and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.

Adverse Reactions: The more common are nausea and edema. Swelling of the ankles or face may be minimized by withholding dietary salt, reduction in dosage or use of diuretics. In elderly patients and in those with hypertension the drug should be discontinued with the appearance of edema. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. The patient should be instructed to take doses immediately before or after meals or with milk to minimize gastric upset. Drug rash occasionally occurs. If it does, promptly discontinue the drug. Agranulocytosis, exfoliative dermatitis, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), or a generalized allergic reaction similar to serum sickness may occur and require permanent withdrawal of medication. Agranulocytosis can occur suddenly in spite of regular, repeated normal white counts. Stomatitis, salivary gland enlargement, vomiting, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported. While not definitely attributable to the drug, a causal relationship cannot be excluded. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, hypersensitivity angiitis, pericarditis and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.



Dosage in Painful Shoulder: Initial: 3 to 6 capsules daily in 3 or 4 equal doses. Trial period: 1 week. Maintenance dosage should not exceed 4 capsules daily; response is often achieved with 1 or 2 capsules daily.

In selecting the appropriate dosage in any specific case, consideration should be given to the patient's weight, general health, age and any other factors influencing drug response. (6)R 46-070-A

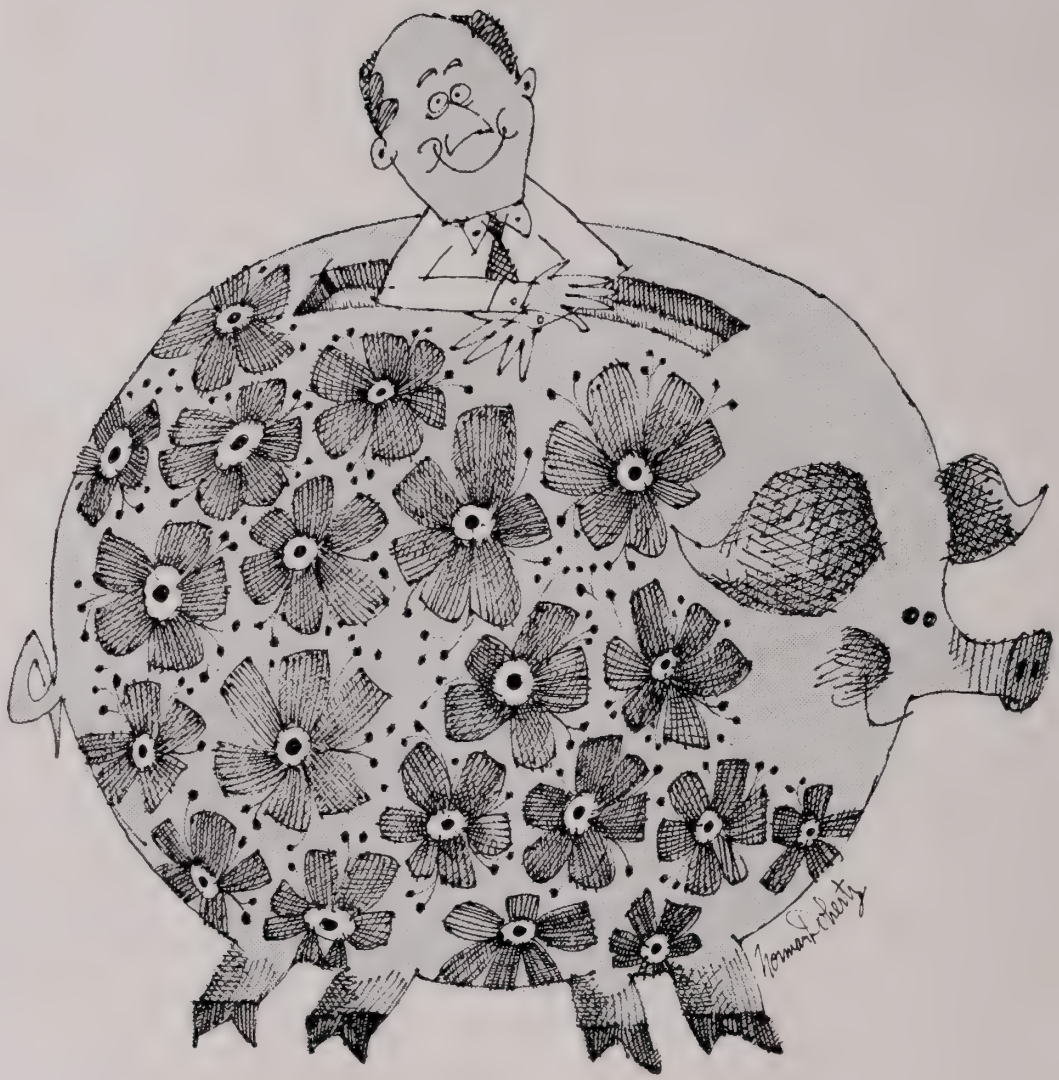
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Myasthenia Gravis*

Emergency Treatment

WILLIAM R. KENNEDY, M.D.†
Minneapolis, Minnesota

MYASTHENIA GRAVIS is one of the few muscle diseases for which adequate therapy is available. The existence of treatment poses an obligation upon the physician to consider this diagnosis in any patient with intermittent muscle weakness.

The initial symptoms appear in the muscles innervated by the cranial nerves. The most frequently encountered symptom is extra-ocular muscle weakness resulting in intermittent diplopia and ptosis. Dysarthria, dysphagia, fatigue of jaw muscles during meals and difficulty holding the head upright are common complaints. Sometimes the weakness is confined to these muscles, but more often the limb muscles become affected. As in most other muscle disorders the proximal girdle muscles are weaker than those located more distally in the extremities. Spontaneous remissions are common.

The diagnosis of myasthenia gravis can usually be made by history and examination, supplemented by the use of pharmacological test substances. Nerve stimulation studies are always useful and sometimes indispensable for confirming the diagnosis. Because the present discussion is restricted to emergency situations, it will be assumed that the diagnosis has been adequately established.

Mechanism

Weakness, the main manifestation of myasthenia gravis, is due to an abnormality of manufacture, transfer or storage of acetylcholine in the nerve terminal portion of the motor endplate. Each nerve impulse triggers the release of acetylcholine from the nerve terminal into the neuromuscular function; this in turn inaugurates depolarization of the muscle membrane. When depolarization reaches a threshold level, a propagated muscle action

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†Assistant Professor, Division of Neurology, University of Minnesota.

potential is initiated and the muscle fiber contracts. But, because the myasthenic nerve terminal releases suboptimal amounts of acetylcholine, arrival of a nerve impulse does not always result in contraction of the muscle fiber. The probability of failure is increased by repetitive nerve stimulation or exercise, both of which cause an increase in the neuromuscular defect which lasts for 15 to 20 minutes. The myasthenic patient requires this time period before strength returns to preexercise levels.

Emergencies

The myasthenic patient becomes involved in emergency situations because of (1) myasthenic crises (too little medication) or (2) cholinergic crises (too much medication).

Myasthenic Crisis

Myasthenic crisis becomes evident as an increase in myasthenic symptoms during a superimposed illness, usually of an infectious nature. The patient notices that the customary dosage of anticholinesterase does not have its usual strengthening action. Then he uses more medication to obtain the desired effect but soon finds the increased dose insufficient.

The onset of ptosis results in a sleepy appearance, sometimes accompanied by compensatory wrinkling of the forehead. Weakness of the jaw muscles causes sagging of the jaw which is supported by the hand. Weakness of the neck muscles may make it difficult to hold up the head. The extremities are also involved, first the proximal hip and shoulder girdle muscles, later the more distal muscles.

Dysarthria, dysphasia, shortness of breath, inability to cough forcefully and weakness of the respiratory muscles lead to bronchitis, pneumonitis and atelectasis. Collapse of the pharyngeal muscles and tongue can cause obstruction of the airway. Death is frequently due to respiratory failure.

Cholinergic Crisis

Cholinergic crisis can be suspected when the patient reports an increase in weakness about one hour after taking anticholinesterase medication. The distribution of weakness produced by overdose is similar to that associated with myasthenia. Certain side reactions also help indicate that excess drug has been taken. These include an increase in salivation and sweating, gastric distress or nausea, abdominal cramps, bradycardia and fasciculation of muscle. Since these reactions are not a consistent feature of cholinergic crisis their absence does not assist in diagnosis. Thus in many cases the cause of crisis remains uncertain.

Treatment

The drugs found to be most useful for treatment are the following anticholinesterases: neostigmine bromide (Prostigmine bromide), pyridostigmine bromide (Mestinon bromide), ambenonium chloride (Mytalase chloride) and edrophonium chloride (Tensilon). These do not enhance release of increased amounts of acetylcholine; they attack the problem indirectly, by slowing destruction of existing acetylcholine, thus allowing it prolonged contact at the muscle membrane. A disadvantage of this type of medication is that acetylcholine in excessive amounts inhibits neuromuscular conduction. The physician must therefore teach the patient to take enough medicine to prevent weakness, yet to avoid an excessive dose, which also induces weakness.

Emergency treatment

The logical treatment at the onset of the sequence of events of myasthenic crisis is to increase anticholinergic medication. However, the drugs often have a diminishing effect because the patient has become refractory to their action. At times it is difficult to determine if more medication is needed or whether the patient has ingested excessive medication and is in cholinergic crisis. The edrophonium chloride (Tensilon) test is often useful in making the distinction. An increase in strength following the intravenous administration of 1-2 mg indicates a need for more anticholinesterase medication. The primary evaluation should center upon the muscles of respiration and those innervated by the cranial nerves. If the improvement is not definite the patient should be presumed to be in cholinergic crisis and all medication discontinued for 72 hours.

Adequate Respiration

Regardless of etiology, the first concern of

the physician should be the establishment of adequate respiration. The patient with advancing weakness must be hospitalized immediately. If there is any indication of respiratory embarrassment tracheotomy should be performed, and if necessary, respiration should be given mechanical assistance. The positive pressure type respirators such as the Bird valve are the most useful. Secretions should be removed frequently by suction. Antibiotics are used prophylactically. Constant competent nursing care is obligatory. Nutrition can be maintained by intravenous feedings or via a gastric tube. If the patient cannot speak or write, a simple communication system using eyeblinks or other movements should be established. After 72 hours, retreatment with anticholinesterase medication is cautiously resumed. The edrophonium chloride (Tensilon) test is useful as a guide to dosage.

Conclusions

The discharged patient must establish close communication with the physician. All illnesses, particularly those of an infectious nature, and any unusual change in requirement for medication must be reported so that future emergencies can be prevented.

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Healing Takes To The Highway

The first doctor trudging out of a primitive settlement to an isolated hut in a forest clearing, and the modern specialist zooming along a cement road in a high-powered car, are both on the same errand. From the very beginning doctors have gone on just such errands. They probably always will. By virtue of their calling the sons of Esculapius are, in a measure, itinerant.

We find physicians among the early settlers on the boats going to Massachusetts and to Jamestown and even the Swedes in Delaware had their barber-surgeon. The Dutch provided not only for preachers and teachers but for "comforters of the sick"—Zieckentrooster—who were often schoolmasters. Penn brought two doctors with him, but Pennsylvania appears to have been a poor place for them in the beginning, for in his diary Gabriel Thomas writes, "Of lawyers and doctors I shall say nothing, because the country is peaceable and healthy." We find them in almost every settlement, however, and when not present, the community depended on barbers, midwives, and the doctors who chanced to be on boats for medical attention.

Many men of affairs took up doctoring as a gentleman's side-line. Governor John Winthrop of Connecticut practiced medicine as an avocation, rode about treating patients in Massachusetts and Rhode Island as well as in his own province, and he even dared prescribe for them by letter. He used a famous cure-all called "rubila." Some of the physicians were storekeepers, some teachers, some parsons. Dr. Abram Staats of New Amsterdam was also a fur trader. Dr. Jasper Gunn of Connecticut practiced surveying and mended kettles to make ends meet between sick calls. Bishop Seabury, the first Anglican Bishop of America, studied medicine as part of the missionary's equipment for Holy Orders. Griffith Owen, a physician who came to America with Penn, visited the neighbouring provinces preaching and healing as well.*

*Richardson Wright: Hawkers and Walkers in Early America, 1927.



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Treatment of Tetanus*

A. B. BAKER, M.D.†
Minneapolis, Minnesota

MOST OF THE current concepts of the pathogenesis of tetanus agree that its development is dependent upon multiplication of the organisms and production of a soluble toxin. It is this toxin which produces the symptoms. According to Abel's experiments, serum therapy is powerless to mitigate or abolish the lethal effect of the tetanus toxin once a certain dose has been fixed by the nervous system. The ideal treatment, therefore, would be to combat the fixed toxin. Such a therapeutic agent is not available. Accordingly, the treatment has centered about controlling the manifestations and preventing their progression to a fatal issue.

Cause of Death

A knowledge of the usual causes of death in this disease is most essential to any consideration of treatment. In tetanus death usually results from one of five causes: namely, spasm of the glottis, with diaphragm and intercostal muscles resulting in asphyxia; toxic encephalitis; exhaustion; medullary failure; secondary pulmonary infection. In a number of cases it is very difficult to distinguish between death from exhaustion and medullary failure; in both there often occur changes in pulse, respiration and temperature. It is our feeling that most fatalities considered due to exhaustion are actually due to unrecognized medullary failure. Pathological studies in a number of our cases tend to lend proof to such a concept.

Treatment

Treatment in tetanus has centered around measures to prevent the above complications.

Excision of the Wound

Since the tetanus bacillus produces its toxin from a focal area, it would seem logical to radically remove the focus of infection and thereby prevent further manufacture of the toxin. Opinions in the literature as to the

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efficacy of this procedure have been controversial. If the present concept of the pathogenesis of this disease is correct, then it would seem to be most essential to radically remove the focus of infection whenever such a focus can be found.

Neutralization of the Circulating Toxin

Opinion has differed with respect to use of serum once symptoms have developed. Experimentally it has been shown that once a lethal dose has been fixed by nervous tissue, antitetanic serum is powerless to mitigate the course of the disease. Since, for practical purposes, it is impossible to determine if this has occurred clinically, it has been thought advisable to give adequate antitoxin to all patients suffering from this disease. A reasonable schedule consists of the administration of 60,000 units during the first 24 hours and 20,000 to 40,000 units daily for the next few days. With the newer tendency to radically remove the focus of infection it would not seem necessary to maintain a high serum level of antitoxin for any length of time. Where the wound is extensive and cannot be completely removed, or where the focus cannot be found, a larger dose and a longer period of administration would logically be indicated.

Intraspinal serum has been gradually discarded because of the dangers in its use and the lack of proof that it has any advantage over the parenteral route.

Sedation

Environmental and pharmacologic sedation has been repeatedly cited as the cornerstone of treatment. Absolute quiet, a dark room and sedation have been considered of great importance in preventing and controlling the muscle hyper-irritability occurring in this disease. The most popular drugs for this purpose have been avertin, the barbiturates, chloral hydrate, paraldehyde and thorazine. The great disadvantage of these drugs is that in the more severe cases, doses which control the symptoms also greatly suppress respiration and predispose to respiratory infections.

Paraldehyde, in our experience, has been one of the best drugs when administered rectally, orally, or intramuscularly with alteration of the routes because of its irritative properties. The dosage must be regulated according to the response of the patient and can frequently be reduced if curare and other such drugs are used concomitantly.

Curare and Curare-like Drugs

It is not surprising that Claude Bernard, who showed that curare had its primary action at the myoneural junction, should have suggested that this substance be used in the treatment of tetanus. The first case was treated in Hoche in 1894. Curare possesses certain theoretical advantages over the sedatives previously used since it permits relaxation without the prolonged respiratory depression and interference with vegetative functions which were present with the usual sedatives. However, the use of curare is somewhat impracticable, since it has to be given intravenously and its action is very short. This necessitates frequent injections and continuous attention by the physician in order to combat toxicity and the side effects of hypersecretion and bronchospasm. A suspension of curare in wax and oil has been used in the treatment of various spastic conditions. We have used intramuscular curare in the treatment of three cases of tetanus. While in all the cases there seemed to be some subjective relief, in only one case was it felt that the amount of sedation required was considerably reduced by the concomitant use of curare.

Penicillin

Knowledge that penicillin inhibited the growth of clostridium tetani naturally stimulated interest in the effect of the antibotic on the disease. It is generally agreed that the organism remains at the site of the wound, multiplies, and produces its toxin locally. However, recovery of the organism from various organs in four fatal cases by Mayer indicates that a bacteremia may occur. Several reports of small series of patients treated with penicillin have been published with statements that in the cases discussed the drug "would seem" to be or "is apparently" life-saving or beneficial. As all were uncontrolled cases, one cannot draw any conclusions from them. Generally, it appears that penicillin has very little effect upon the disease itself. Use of this drug is of utmost importance, however, in combating the secondary pulmonary complications that often prove fatal. It is for this purpose that

we have instituted the routine use of penicillin in all cases of tetanus admitted within the past few years.

Tracheotomy and Oxygen Therapy

In 1942 Baker demonstrated marked nerve cell changes in certain cell groups in the medulla in tetanus. While the clinical signs and the mode of death in this disease had often seemed consistent with medullary failure, this cause had previously been given little consideration. Moreover, even under the best regulation of sedation it is often impossible to totally avoid acute laryngospasm which acts as a constant threat of death from asphyxia and can seldom be averted by intubation because of the coincident trismus. We are convinced that the institution of early tracheotomy and supplemental oxygen therapy have been of great value in preventing this occurrence. Accordingly we have instituted early tracheotomy in order to avoid hypoxia to the medulla and to insure an adequate airway in the event of spasm of the laryngeal muscles. Also the presence of a tracheotomy facilitates the administration of continuous oxygen, thus giving an added safety factor. We wish to emphasize the early and elective nature of this procedure.

The Doctor

There are men and classes of men that stand above the common herd: the soldier, the sailor, and the shepherd not infrequently; the artist rarely; rarelier still, the clergyman; the physician almost as a rule. He is the flower (such as it is) of our civilization; and when the stage of man is done with, and only to be marvelled at in history, he will be thought to have shared as little as any in the defects of the period, and most notably exhibited the virtues of the race. Generosity he has, such as is possible to those who practice an art, never to those who drive a trade; discretion, tested by a hundred secrets; tact, tried in a thousand embarassments; and what are more important, Heraclean cheerfulness and courage.*

*Robert Louis Stevenson

Soul

O who shall, from this Dungeon, raise,
A soul inslav'd so many ways?
With bolts of Bones, that fetter'd stands
In Feet; and manacled in Hands.
Here blinded with an Eye; and there
Deaf with the drumming of an Ear.
A Soul hung up, as 'twere, in Chains
Of Nerves, and Arteries, and Veins.
Tortured, besides each other part,
In a vain Head, and double Heart.

—Marvell

News is anything that makes a woman say, "For heaven's sake!"—Ed Howe

---

One's eyes are what one is; one's mouth, what one becomes—Galsworthy

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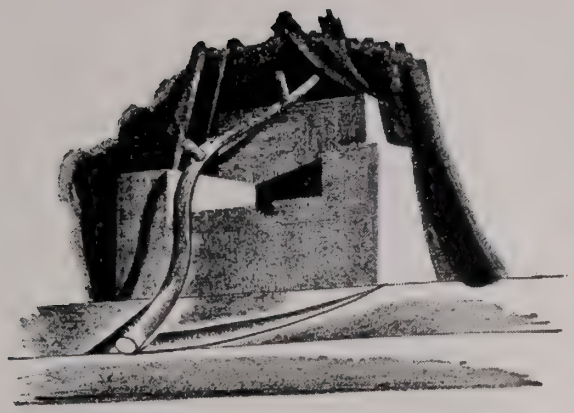
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In Memoriam

Thou know'st 'tis common; all that lives must die,
Passing through nature to eternity.—Shakespeare

FREDERICK A. LOVE, M.D.

Dr. Frederick A. Love, 80, who for more than 50 years practiced medicine in Carlos, died June 5. Born in Preston, Dr. Love attended Hamline University and completed his medical training at the University of Minnesota.

He was a member of the American Medical Association and the Park Region District and County Medical Society and a 50 Club and Life Member of the Minnesota State Medical Association.

He is survived by his wife, a daughter and two sons.

RUDOLPH E. HULTKRANS, M.D.

Dr. Rudolph E. Hultkrans, 68, Minneapolis surgeon, died June 12. Dr. Hultkrans attended the University of Minnesota and received his medical degree in 1926.

He was a member of the American Medical Association, the Hennepin County Medical Society and an Associate Member of the Minnesota State Medical Association.

He is survived by his wife and a son.

WALDEMAR G. JOHANSON, M.D.

Dr. Waldemar G. Johanson, 62, St. Paul physician, died June 18 in Bethesda Hospital after a heart attack. Dr. Johanson practiced medicine as a family doctor for 36 years on Payne Avenue and the East Side.

He was a graduate of the University of Minnesota Medical School and a member of the Ramsey County Medical Society, the American Medical Association and the Minnesota State Medical Association. Dr. Johanson was also a member of the Ramsey County Historical Society, the Minnesota Historical Society, the American Swedish Institute and the American Swedish Pioneer Historical Society.

He is survived by his wife, two daughters and one son.

ROY M. MAYNE, M.D.

Dr. Roy M. Mayne, tuberculosis specialist, died May 25. Born in Shelby, Iowa, Dr. Mayne attended the State University of Iowa, College of Medicine, and received his degree in 1921. In 1927 he joined the staff at the Nopeming Sanatorium, Nopeming, Minnesota.

He was a member of the American Medical Association and St. Louis County Medical Society and an Associate Member of the Minnesota State Medical Association.

He is survived by his wife, a daughter and two sons, one of whom is Dr. John G. Mayne of Rochester.

RICHARD BARDON, M.D.

Dr. Richard Bardon, 71, Duluth physician, died June 3, after a brief illness. He was born in Superior, Wisconsin, and attended Northwestern University Medical School, Chicago, graduating in 1924.

For some years, Dr. Bardon was chairman of the Duluth Diabetes Detection Drive and had served as chief of staff of St. Mary's and Miller Memorial hospitals. He was a member of the American Medical Association, the American College of Physicians, the American Diabetes Association, the Minnesota Society of Internal Medicine, the St. Louis County Medical Society, and the Minnesota State Medical Association. A recognized authority on local and Northern Minnesota history, Dr. Bardon was president of the St. Louis County Historical Society for 17 years and a member of the board of the Minnesota State Historical Society. He co-authored a historical book on early Minnesota fur traders, entitled "Fur Traders Reminiscences."

He is survived by his wife and three sons.

MARGUERITE SCHWYZER, M.D.

Dr. Marguerite Schwyzer, 58, St. Paul physician, died unexpectedly of pneumonia, in Zurich, Switzerland. She had been traveling abroad for about a month.

Born in St. Paul, she had practiced medicine in St. Paul for a number of years. In recent years her practice was with the University of Minnesota Student Health Service and the Wilder Foundation.

In 1960 she worked with Dr. Tom Dooley's "Medico" team in Haiti in the Caribbean and at one time had lived in Europe, Africa and Asia.

She is a member of the American Medical Association, the Minnesota State Medical Association and the Ramsey County Medical Society.

Dr. Schwyzer is survived by two brothers, Dr. Arnold Schwyzer, Bronxville, New York, and Dr. Hanns Schwyzer, Raton, New Mexico.

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Replies to advertisements with key numbers should be mailed in care of Minnesota Medicine, 375 Jackson, St. Paul, Minn. 55101.

GENERAL PRACTITIONER: Serve as Medical Director of 50-bed Minnesota State Prison Hospital; staff of registered nurses, surgical nurse, laboratory technician, dentist, and consultants with various specialties; surgical residents provided by University of Minnesota Hospitals; salary $20,800 to $27,800 based on experience and qualifications; benefits include hospitalization and life insurance, vacation and sick leave accruals, liberal retirement program; located in Stillwater, Minnesota, in the recreational St. Croix River Valley; 30 minutes from Minneapolis-St. Paul by freeway. Contact Personnel Department, Box 55, Stillwater, Minnesota 55882.

GENERALIST as member of Medical Staff of progressive State Hospital in Michigan's Vacationland. Hospital has 3-year accreditation. JCAH and 3-year residency accreditation by A.P.A. Salary $17,867.20 to $21,777.60. Excellent fringe benefits. Civil Service security when qualified. Apply L. B. Young, M.D. Director of Medical Services, Traverse City State Hospital, Traverse City, Michigan 49684.

ST. PAUL: Spacious suite in new split-level building, partitioned for medical offices. Other level occupied by dentist. Excellent location adjacent to large shopping center. 1504 White Bear Avenue, 774-7144.

THREE MAN group in North West Wisconsin Resort, State Conservation and Retirement Area needs two more physicians adequately to serve their practice. Facilities offered are three-room physician suites, X-ray and lab under AMT technician, RN-only nursing personnel. New accredited thirty-two bed hospital and forty-six bed nursing home. Deer and duck hunting, fishing within five minutes of town. Internist most needed; generalists welcomed. Will meet any reasonable salary request. Partnership after one year. Write: MINNESOTA MEDICINE—365; 375 Jackson St., St. Paul 55101.

WANTED: G.P. or Internist willing to do some G.P. Twin-towns totalling 12,000 western Minnesota Group now two G.P.'s and one FRCS surgeon. Modern clinic building with eight assistants, X-ray and minor laboratory, 125 bed accredited hospital. Rotating calls one night a week and every fifth week-end. Hunting, fishing, golfing available. Initial salary $1,500 per month. Opportunity for partnership in one year. Apply to Louis T. O'Brien, M.D., Breckenridge, Minnesota.

SKIING, HUNTING, FISHING and practice of Internal Medicine offered to board qualified or certified internist by 21 man specialty clinic in northern Minnesota. Presently adding new modern facilities to keep up with rapidly expanding economy. Salary first year, shareholder status second year. Reply Russell Anderson, M.D., East Range Clinics, Ltd., Virginia 55792 or call collect, Area Code 218, 741-6244.

DIRECTOR OF MEDICAL EDUCATION, full time —Methodist Hospital, St. Louis Park, Minnesota 55426. Contact Mr. Earl Dresser, Administrator or Dr. W. John Dawson, acting director of medical education.

GENERAL SURGEON interested in some general practice to associate with a 2-man partnership in a rich agricultural community in southern Minnesota. Modern hospital and new clinic building. Hunting, 9-hole golf course, swimming pool. Salary open and full partnership as soon as desired. Write: Minnesota Medicine—405, 375 Jackson, St. Paul 55101.

WANTED General practitioner, to join two G.P.'s well established in north central Minnesota community 2200 pop., 65 miles from Twin Cities. Excellent office space with lab and X-ray, just opened new hospital all facilities. Assistantship or partnership. Considerable surgery and obstetrics. Hunting, fishing, golf club. Great opening for interested G.P. WRITE MINNESOTA MEDICINE—381; 375 Jackson. St. Paul 55101.

INTERNIST AND GENERAL PRACTITIONER wanted to join a five-man clinic group in Minneapolis. Complete laboratory and X-ray with board roentgenologist. Excellent hospital staff associations. Salary arrangement to start with, early partnership. Write MINNESOTA MEDICINE—289; 375 Jackson, St. Paul, 55101.

PRACTICE FOR SALE: Well established general practice in South Minneapolis serving an excellent community, within easy reach of the finest hospitals in the State. Very reasonable, low overhead. Splendid opportunity for solo or partnership practice. Write: MINNESOTA MEDICINE-397, 375 Jackson St., St. Paul 55101.

GENERAL SURGEON, Certified, part or full-time association in multi-specialty clinic. Alfred F. Anderegg, M.D., 645-5851, 2500 Como Ave., St. Paul, Minnesota.

WANTED: G.P. to join clinic serving population area of 12,000. City has new hospital, new clinic building, two nursing homes, new Jr-Sr high school, new swimming pool, rich farming area in Red River Valley. Fishing and hunting nearby; metropolitan city close by. Salary open and partnership if interested. Write or call Warren Clinic, Warren, Minnesota 742-6231, area code 218.

GENERAL PRACTITIONER wanted to join well-established practitioner. New clinic building—90 miles east of St. Paul—city of 14,000. Early partnership with full hospital facilities. Ideal location. L. W. Picotte, M.D.; Chippewa Falls, Wisconsin.

PRACTICE AVAILABLE: A well-established general practice of 36 years in south Minneapolis with a well equipped office. Must retire because of physical disability. If interested phone 822-0493 after 7:00 P.M. any day, or write MINNESOTA MEDICINE 411; 375 Jackson, St. Paul, Minnesota 55101.

(Continued to Page 1308)



NORTHLANDS REGIONAL MEDICAL PROGRAM

REGIONAL PROGRAM FOR HEART DISEASE, CANCER AND STROKE

The Operational Program Application

On July 30, we sent twenty copies of a large document, the first Operational Grant Request, to the Division of Regional Medical Programs in Bethesda, Maryland. Our goal is to fulfill the requirements to move from the "talking phase" (planning) to the "doing phase" (operational), starting January 1, 1969. The 1000 page operational grant application testifies to the eight months of intensive effort culminating in approval by the 41-member Regional Advisory Group on July 26, 1968.

"Operational Readiness" required concurrent development of the following four components:

A Responsible Grantee Organization

The law requires effective cooperative arrangements between the medical centers and peripheral health care organizations and personnel. Northlands Regional Medical Program was incorporated as a non-profit corporation on July 1. By-Laws were adopted on July 9. A "Guarantee of Support" of $10,000 was obtained from each of the nine sponsoring organizations to establish fiscal responsibility. The processes necessary to achieve these results were tedious and difficult. Like feminine charm, intimate performance is more difficult to achieve than overt appearance and pronouncement.

Effective Planning for Action

The law requires that component projects in the program be based on demonstration of needs, resources, objectives and priorities. This process required two steps—first, formulation of planning documents representing consensus opinions on planning for the program; and second, effective review and decision regarding a total of 22 projects which were proposed for inclusion. Twelve committees and sub-committees of five to seven men each (a total of 62 professional persons) spent a total of 117 man days in 29 meetings, varying in duration from one-half to two days, to carry out this component. The individual home study time and the many days of NRMP staff time represents significant, untabulated additional efforts. The committees were remarkably dedicated and conscientious in their deliberations. Project proposers were not given an opportunity to personally come before review committees, to avoid personal pressures. Like Judeo-Christianity, the idealism of health care institutions and personnel is put to the crucial test when funding of personal or institutional interests is concerned.

Effective Direction by the Board of Trustees

The success or failure of the corporation is ultimately determined by the effectiveness of its Board of Trustees. The Board of Northlands Regional Medical Program spent many long hours in development of the Articles of Incorporation, By-Laws, new Regional Advisory Group plus review of all project proposals.

The philosophy of Regional Medical Programs is new to all of us. Decision-making involves controversy. Continuing readjustment and self-renewal are required. As in marriage, partners on a Board are often the severest critics of each other.

Formation of and Approval by a "Regional Advisory Group"

The law requires "veto-type" power to be vested in an advisory committee representing all health care interests in the region. A new Regional Advisory Group of 41 voting and 15 non-voting members was created. By-Laws were formulated. Two all-day meetings were held on May 25 and July 26. Approval of the program on July 26 followed advance home review of some 800 pages of material and a long day of presentation of summaries. Some members were unhappy with the complexity and magnitude of the presentation compared to the time for discussion. Advisors are frequently called upon to help carry out the most difficult assignments in a minimum of time.

The operational grant application represents consensus agreements involving a total of 107 voluntary leaders in health care activities, a full-time staff of ten in the central organization and a part-time staff of five in the medical centers. One hundred and twenty-two leaders also constitute 122 critics. Consensus approval was a difficult but significant achievement. We believe the proposed program is a good one and we are proud to present it to the Division of Regional Medical Programs. The program contains the following:

1. Four Core Proposals for overall development and operation—Central Organization; University of Minnesota; Mayo Foundation; and American Rehabilitation Foundation.
2. Intensive Coronary Care Unit Project—Minnesota Heart Association, H. T. Mankin, M.D., Director.
3. Postgraduate Education in Pediatric Cardiology—University of Minnesota, R. V. Lucas, M.D., Director.
4. Education and Clinical Evaluation in Coronary Heart Disease—Mayo Clinic, R. C. Bahn, M.D., Director.
5. Diabetes Regional Center—Diabetes Research Foundation, D. D. Etzwiler, M.D.
6. Pilot Phase Regional Cancer Registry—Northlands Regional Medical Program, V A. Gilbertson, M.D., Director.
7. Stroke Rehabilitation Through Education—American Rehabilitation Foundation, J. A. Anderson, M.D., Director
8. Stroke Rehabilitation Management Simulator—American Rehabilitation Foundation, L. R. Leslie, M.D., Director.
9. Pilot Program of Continuing Medical Education—Mayo Clinic, C. F. Code, M.D.
10. Postgraduate Education in Diseases of Childhood—University of Minnesota, J A. Anderson, M.D., Director.
11. Dial-Access Medical Library—Northlands Regional Medical Program, L. G. Berglund, B.A., Director.
12. Planning Program for Heart, Cancer and Stroke—Saint Paul Bureau of Health. B. L. Levich, Director.

The application will now be subjected to intensive review by the Division of Regional Medical Programs. This will include a two to three-day site visit by a peer group team of leaders in health care fields. Final decision will rest with the National Advisory Council at its meeting on November 28.

Winston R. Miller, M.D., F.A.C.P.
Program Director



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Contraindications: Hypersensitivity to any component.

Warning: In renal impairment, since liver toxicity is possible, lower doses are indicated; during prolonged therapy consider serum level determinations. Photodynamic reaction to sunlight may occur in hypersensitive persons. Photosensitive individuals should avoid exposure; discontinue treatment if skin discomfort occurs.

Precautions: Drowsiness, anorexia, slight gastric distress can occur. In excessive drowsiness, consider longer dosage intervals. Persons on full dosage should not operate vehicles. Nonsusceptible organisms may overgrow; treat superinfection appropriately. Treat beta-hemolytic streptococcal infections at least 10 days to help prevent rheumatic fever or acute glomerulonephritis. Tetracycline may form a stable calcium complex in bone-forming tissue and may cause dental staining during tooth development (last half of pregnancy, neonatal period, infancy, early childhood).

Adverse Reactions: *Gastrointestinal*—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. *Skin*—maculopapular and erythematous rashes; exfoliative dermatitis; photosensitivity; onycholysis, nail discoloration. *Kidney*—dose-related rise in BUN. *Hypersensitivity* reactions—urticaria, angioneurotic edema, anaphylaxis. *Intracranial*—bulging fontanels in young infants. *Teeth*—yellow-brown staining; enamel hypoplasia. *Blood*—anemia, thrombocytopenic purpura, neutropenia, eosinophilia. *Liver*—cholestasis at high dosage.

Upon adverse reaction, stop medication and treat appropriately.

Lederle

349-8



Meetings and Announcements

The more we study, the more we discover our ignorance.—SHELLEY.

SEPTEMBER

Scott-Carver County Medical Society
County Society Meeting, 6:30 p.m., Wagner's Supper Club, September 3, Jordan.

Zumbro Valley Medical Society
Regular Meeting, Plummer Hall, September 4, 7:00 p.m., Rochester.

Minnesota Radiological Society
Fall Meeting, Cragun's on Pine Beach; Scientific Session, September 6-8, 2:00 p.m. (7th), Gull Lake, Brainerd.

Upper Mississippi Medical Society
Regular Fall Meeting, 2:00 p.m., Driftwood Lodge, September 7, Whitefish Lake, Pine River.

Southwestern Minnesota Medical Society
Ellers Supper Club, September 9, 7:00 p.m., Worthington.

Camp Release District Medical Society
Hunt Hotel, Montevideo, September 12, 7:30 p.m.

St. Louis County Medical Society
Executive Meeting, September 12, 6:00 p.m., St. Luke's Hospital, Regular Meeting at 8:00 p.m.

Minnesota-Dakota-Manitoba Orthopedic Society, September 13-14, Rapid City, South Dakota.

Minnesota Chapter-American Academy of General Practice, September 13-20, National Meeting, Las Vegas, Nevada.

Headwaters Medical Society
Annual Meeting, September 14, 3:00 p.m., Bemidji Hospital.

McLeod County Medical Society
Der Erl Konig, Glencoe, September 17, 6:30 p.m.

Renville-Redwood County Medical Society
Redwood Falls Golf Club, September 17, 7:00 p.m.

Steele County Medical Society
Regular Meeting, Inn Towne Motel, September 17, 6:30 p.m.

West Central Minnesota Medical Society
Regular Meeting and Speaker, Minnewaska House, Glenwood, September 17 or 24, 7:30 p.m.

Blue Earth Valley Medical Society
Interlaken Golf Club, Fairmont, September 18, 7:00 p.m.

Kandiyohi-Swift-Meeker County Medical Society
Westwood Inn, Spicer, September 19, 7:00 p.m.

Twin City Urological Society
Town and Country Club, September 20, 6:00 p.m.

Blue Earth County Medical Society
Century Club, September 23, 6:00 p.m.

Lyon-Lincoln County Medical Society
Physicians host Attorneys in joint meeting, 6:30 p.m., September 24, Chalet Club, Marshall.

Range Medical Society
Executive Committee, September 24, 6:00 p.m., Hibbing; General meeting & dinner, 7:15 p.m.

Minnesota Chapter-American Academy of Pediatrics
Dinner meeting, Town & Country Club, St. Paul, September 26, 6:30 p.m.

Northwestern Pediatric Society
Hudson House, Hudson, Wisconsin, September 27, 9:00 a.m.

Minnesota Society of Anesthesiologists
Fall Scientific Meeting, evening, September 28.

Ramsey County Medical Society
Regular Meeting, 1500 Lowry Medical Arts Building, St. Paul, September 30, 8:00 p.m.

Waseca County Medical Society
Regular Meeting, September 30.

Tenth Annual Methodist Hospital Symposium

The tenth annual symposium, sponsored by the Methodist Hospital medical staff, will be held on Saturday, September 14, 1968, in the Methodist Hospital auditorium.

The subject for this coming year's symposium will be on current concepts and treatment of "shock."

The Minnesota Academy of General Practice has approved this symposium for six prescribed hours of credit.

There is no registration fee for the scientific sessions or the noon luncheon. All physicians are most cordially invited to attend. For additional information please contact Mrs. Audrey Engstrom, medical staff secretary, 929-1313.

Sixth National Cancer Conference

Conference will be held September 18-20 in Denver, Colorado. For full information contact: American Cancer Society, 3702 E. Lake Street, Minneapolis. Phone 722-6614. Subjects to be discussed are cancer of the female pelvis, gastrointestinal tract, skin, neck and head, and lung. Also to be discussed are skeletal tumors, soft part tumors and basic problems and advances in cancer chemotherapy and hormone therapy.

(Continued from page 1302)

THE WEST MEDICAL CLINIC has an opening for a General Practice Physician, on October 1, 1968. This is a five man group that conducts a practice near downtown St. Paul and also, has the Airport Medical Clinic at Wold Chamberlain Field, Twin City International Airport. Both clinics have full laboratory and x-ray services with technologists covering both fields.

The Airport Medical Clinic does industrial, occupational and Aviation medicine. FAA examinations are conducted at both clinics.

The clinic located near downtown St. Paul has a practice limited principally to internal medicine, pediatrics, as well as occupational and industrial medicine. There is only a limited practice of obstetrics and no surgery.

Salary is open and opportunity for partnership is available. Write: West Medical Clinic, 539 W. Seventh Street, St. Paul, Minnesota 55102. Phone: Area Code 612-227-9341.

ANOKA-MINNEAPOLIS excellent openings for psychiatrist—unit chief & staff physicians. 600-bed open-door hospital. Salary $16-$28,500. Apply Medical Director, Anoka State Hospital, Anoka, Minnesota 55303.

DOCTOR WANTED in Fairfax, Minnesota. Clinic building available. Present doctor leaving. This is an excellent opportunity. Please contact Dr. Glenn Nelson or Leo Keller at Fairfax.

FOR SALE: Rarely used manual Ritter Multi-purpose proctoscopic table—Model 3—Type 7. Purchase price when new $1,400.00. Best offer takes table. Telephone Mrs. Asmus 645-1195 or write Mrs. Asmus at 393 North Dunlap Street, 231 Central Medical Bldg., St. Paul 55104.

PSYCHIATRIST—board eligible, desires association with individual or group in Twin Cities area. Eight years experience in general and forensic psychiatry. Write MINNESOTA MEDICINE-413, 375 Jackson St., St. Paul 55101.

FAMILY PHYSICIAN wanted for an association with a clinic in the Minneapolis suburban area. Excellent hospital, school, churches, and living facilities available. Write Drs. T. J. Bloedel and H. R. Ransom, 226 Central Ave., Osseo, Minnesota, or telephone 425-2118 collect.

TWO MAN GROUP needs a third general practitioner in a fast-growing West St. Paul area. Begin with salary and assume early partnership. Contact N. W. Howe, M.D., or E. J. McEllistrem, M.D., 1246 Gorman—West St. Paul. Minn. 55118 Telephone: 224-8001.

WANTED: Physician for ward and/or clinic in accredited State Mental Hospital in fishing and hunting area of Minnesota. Should have interest though not necessarily experience in mental health and illness. Living quarters provided. Send vita with application. Not a retirement position. Older physicians with good credentials acceptable. Write: MINNESOTA MEDICINE-414, 375 Jackson St., St. Paul 55101.

DESIRE TO GIVE away a general surgery practice which should immediately provide a versatile surgeon with 200 majors annually and unlimited ceiling. Will provide modern office facilities in a ten-year-old clinic building and guarantee a minimum income with no strings attached. Should be board qualified and under forty-five. Excellent hospital facilities with resident anesthesiologist and pathologist. Reason:—desire to limit my practice to Urology. Write or call O. K. Behr, M.D., 407 North Broadway, Crookston, Minnesota—Area Code 218-281-3210.

WANTED BY TWO INTERNISTS—a Board Eligible or Board Certified Internist to practice in the Twin City area. Excellent opportunity and early partnership. Write: MINNESOTA MEDICINE-407, 375 Jackson, St. Paul, 55101.

WANTED: General practitioner to join two young general practitioners in well-established practice in suburban St. Paul. Excellent office space with lab, x-ray, and emergency room. Salary negotiable, with an association leading to early partnership opportunity. Write MINNESOTA MEDICINE 412, 375 Jackson St., St. Paul 55102.

FOR RENT: 14-room deluxe clinic in shopping center—Robbinsdale. 5 min. from Glenwood Hills and No. Memorial Hospitals—3 months rent free—will subdivide—36th Ave. No. and Noble—Noble Drug, JU 8-9449—Ben or Lou.

EIGHTEEN-MAN Wisconsin group located in college community of 40,000 with excellent hospital facilities is seeking additional associates in the following areas: (1) Internal Medicine, (2) Urology, (3) General Surgery, (4) General Practice, and (5) Pediatrics. For further information please contact D. R. Griffith, M.D., Midelfort Clinic, Eau Claire, Wisconsin 54701.

ASSOCIATE urgently needed in busy general practice. Excellent clinic and hospital facilities. Salary open. Partnership after 1 year. Klefstad Clinic, Greenbush, Minn. Call collect: Lloyd H. Klefstad, M.D., Tele. 218-782-5275 or 4725.

Heart Symposium

"Cardiovascular Disease—Practice, Problems, Progress" is the theme of a two day Great Plains Heart Associations Symposium, to be held at the Sheraton-Ritz Hotel in Minneapolis on Friday, September 27, and Saturday, September 28, 1968. Host State for the Symposium will be the Minnesota Heart Association. There will be Curbside Sessions on specialized techniques, remedial heart disease, hypertension, diagnosis and management of stroke, cardiovascular drugs, and pulmonary embolism: diagnosis, medical and surgical management. Attendees are encouraged to bring along electrocardiograms for discussion. For more information contact the Minnesota Heart Association, 1821 University Ave, St. Paul.

Sources of sinus headache



REGION OF SENSATION

FRONTAL SINUS—headache localized over the frontal region, commonly beginning in the morning. Eyes painful to touch, may be slight swelling over eyes, puffy eyelids.

SPHENOID SINUS—most difficult to diagnose. Headache or sense of pressure over vertex. May be pain in ear or mastoid region.



MAXILLARY SINUS—headache and tenderness under eyes at top of cheekbones, usually starting in early afternoon. Possible swelling of cheek. Pain in jaw and back teeth.

ETHMOID SINUS—headache, tightness in upper part of bridge of nose and well down its sides. Pain, deep-seated behind the eyes and in inner corners of the eyes.



TURBINATES—pain along medial and lateral walls of the inside of the nose. Headache in frontal region, along supraorbital ridge, a feeling of fullness in the head.

Source of symptomatic relief

SINUTAB



Sinus headache is often a reflection of congestion in the nasal mucosa. The pain that results in the various regions of the head may help in determining the particular structure(s) responsible. The Sinutab formula is specifically designed for symptomatic relief of sinus headache and nasal congestion. **Sinutab** *not only* **provides an effective decongestant** — to reduce mucosal engorgement and facilitate freer breathing — *and* **an antihistamine** — to help reduce edema and excessive secretions — but it *also* provides, in contrast to other leading decongestants, **two analgesics** for immediate relief of pain and discomfort.

And, too, the Sinutab dosage schedule of 2 tablets, *q.* 4 *h.* permits controlled and continuing analgesic relief.

Adverse Reactions: Epigastric distress, drowsiness, dizziness, insomnia and nervousness.

Precautions: Instruct patients not to drive or operate machinery if drowsiness occurs. Use with caution in patients with thyroid disease, heart disease, hypertension, diabetes or kidney disease. Excessive dosage or prolonged use may cause kidney damage.

Dosage: Adults—2 tablets every 4 hours.

Each tablet contains 150 mg. acetaminophen, 150 mg. phenacetin, 25 mg. phenylpropanolamine HCl, and 22 mg. phenyltoloxamine citrate.

SPECIFIC FORMULA **SINUTAB**® FOR SINUS HEADACHE

Also Available on Prescription:

Sinutab® with Codeine.* Each tablet contains 15 mg. (¼ gr.) codeine phosphate (Warning: May be habit forming), 150 mg. acetaminophen, 150 mg. phenacetin, 25 mg. phenylpropanolamine HCl, and 22 mg. phenyltoloxamine citrate.

Sinutab® Pediatric Suspension. Each 5 ml. teaspoonful contains 300 mg. acetaminophen, 12.5 mg. phenylpropanolamine HCl, and 10 mg. phenyltoloxamine citrate.

*Subject to Federal Narcotics Regulations.

For 1 complimentary bottle of 30 Sinutab tablets, write: J. S. Travis, Warner-Chilcott Laboratories, Morris Plains, N.J. 07950. Please mention this journal.

S-IN-81-4C

WC **WARNER-CHILCOTT** Morris Plains, N.J.



Physician's Diary

It's the daily grind that gives a man polish.—National Safety News

Doctors Paul G. Quie, Robert A. Good, Justin J. Wolfson, Stefan D. Laxdal, Hans Kuisk, Jose B. Sanchez, Stephen A. Kieffer, Kirt Amplatz, Harold O. Peterson and **Yosh Maruyama** presented medical papers to the Radiological Society of North America, which held its annual meeting in Chicago recently.

* * *

Dr. John E. Smith, Edina, has been elected president of the St. Barnabas Hospital Medical Staff.

* * *

Dr. T. G. Martens, Mayo Clinic ophthalmologist and otolaryngologist, is the newly elected president of the Minnesota Academy of Ophthalmology and Otolaryngology. He will take over the office January 1, 1969.

* * *

After retiring from private practice in St. James on May 1, **Dr. A. D. Mattson** is with the Minnesota Department of Welfare in the reorganization of the staff at Faribault State Hospital.

* * *

Dr. Kristofer Hagen, Edina, served in South Vietnam for two months with the American Medical Association Volunteer Physicians for Vietnam.

* * *

Dr. Jeannette L. Baker has been named to succeed **Dr. W. L. Patterson** as medical director of the Fergus Falls State Hospital.

* * *

Dr. Edward Mandell, Director of the Veterans Administration Hospital, Minneapolis, retired recently.

* * *

Newly elected officers of the Minnesota Academy of General Practice are **Dr. Matt Plasha,** Coon Rapids, president, **Dr. Wallace Mathews,** Mankato, president-elect, **Dr. John W. Lester,** Mapleton, vice-president and chairman of the board of directors, and **Dr. C. A. Anderson,** Hector, secretary-treasurer.

* * *

Dr. Tracy E. Barber, Austin, has been named treasurer of the Industrial Medical Association, international association of physicians of industry.

New Locations: **Dr. L. J. Hoyer** has left Windom to take a position in the general medical and surgical department of the Winnebago State Hospital in Winnebago, Wisconsin. . . . **Dr. Kent Hardy,** Mayo Graduate School resident in dermatology, has served in Afghanistan for three months with MEDICO, a service of CARE. . . . **Dr. John Mathers,** now at the Austin Clinic, began a sabbatical leave of one or two years in July to become teacher and consultant in the Department of Obstetrics and Gynecology in the Okinawa and Central Hospital near Naha, Okinawa. . . . **Dr. Robert L. Hegrenes** will leave Farmington to join the Hutchinson Medical Center in Hutchinson. . . . **Dr. Benigno Buentipo** will begin practice in Wheaton. . . . **Dr. Ben M. Tuma,** formerly of Montgomery, has joined the Alexandria Clinic. . . . **Dr. Curtis A. Johnson** has left Waseca to join **Dr. George Bingham** in Olivia where a new clinic is to be completed. . . . **Dr. Martin Raymond Swersky** will become a medical officer of the U.S. Public Health Service Indian Hospital in Cass Lake.

* * *

Several Minnesota physicians have been named by the American Academy of Pediatrics to evaluate the medical aspects of Head Start Programs. They are **Drs. Albertus F. Dodson,** Brainerd, **Robert Hodapp,** Willmar, **David Bloom,** Golden Valley, **Curtis M. Johnson,** Winona, and **Edmund Burke,** Rochester.

* * *

The second Pioneer Award of the Northwestern Mental Health Center was presented to **Dr. Clifford Stadem,** Crookston, former chairman of the Mental Health Center Board. The award was presented in appreciation for his continued guidance to the Mental Health Board.

* * *

Richard O. Zocher has been appointed Administrator of St. Croixdale Hospital, Inc., in Prescott, Wisconsin. Prior to his appointment, Mr. Zocher was associated with Mounds Park Hospital in St. Paul for eight years as Business Manager.



Tandearil® in Osteoarthritis
oxyphenbutazone

Contraindications: Edema; danger of cardiac decompensation; history or symptoms of peptic ulcer; renal, hepatic or cardiac damage; history of drug allergy; history of blood dyscrasia. The drug should not be given when the patient is senile or when other potent drugs are given concurrently.
Warning: Tandearil is an analog of phenylbutazone; sensitive patients may be cross-reactive. If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Instances of severe bleeding have occurred. Persistent or severe dyspepsia may indicate peptic ulcer; perform upper gastrointestinal x-ray diagnostic tests if drug is continued. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy. Use with caution in the first trimester of pregnancy and in patients with thyroid disease.
Precautions: Before prescribing, carefully select patients, avoiding those responsive to routine measures as well as contraindicated patients. Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patient should not exceed recommended dosage, should be closely supervised and should be warned to discontinue the drug and report immediately if fever, sore throat, or mouth lesions (symptoms of blood dyscrasia), sudden weight gain (water retention), skin reactions, black or tarry stools or other evidence of intestinal hemorrhage occur. Make complete blood counts at weekly intervals during early therapy and at 2-week intervals thereafter. Discontinue the drug immediately and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.
Adverse Reactions: The more common are nausea and edema. Swelling of the ankles or face may be minimized by withholding dietary salt, reduction in dosage or use of diuretics. In elderly patients and in those with hypertension, the drug should be discontinued with the appearance of edema. The drug has been associated with peptic ulcer and may reacti-

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vate a latent peptic ulcer. The patient should be instructed to take doses immediately after meals or with milk to minimize gastric upset. Drug rash occasionally occurs. If it does, promptly discontinue the drug. Agranulocytosis, exfoliative dermatitis, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis) or a generalized allergic reaction similar to a serum sickness syndrome may occur and require permanent withdrawal of medication. Agranulocytosis can occur suddenly in spite of regular, repeated normal white counts. Stomatitis, salivary gland enlargement, vomiting, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported. While not definitely attributable to the drug, a causal relationship cannot be excluded. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, hypersensitivity, angiitis, pericarditis and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.

For complete details, please see full Prescribing Information.

Dosage in Osteoarthritis: Initial: 3 to 6 tablets daily in divided doses. Usually unnecessary to exceed 4 tablets daily. A trial period of one week is considered adequate to determine the therapeutic effect of the drug. Maintenance: Effective level often achieved with 1 or 2 tablets daily, should not exceed 4 tablets daily. In selecting appropriate dosage in any specific case, consideration should be given to the patient's weight, general health, age and other factors influencing drug response. Availability: Tan, round, sugar-coated tablets of 100 mg. in bottles of 100 and 1000.

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England Autumn

C. F. Yeager, M.D.

OCTOBER, 1968

Sources of Sinus Headache

Sinus headache is often a reflection of congestion in the nasal mucosa. The pain that results in the various regions of the head may help in determining the particular structure(s) responsible. The proved formula of Sinutab which provides triple action — analgesic, decongestant and antihistaminic — is specifically designed for the symptomatic relief of sinus headache and nasal congestion.

INDICATIONS: Sinutab is indicated for the symptomatic relief of headache, facial pain, malaise, fever, nasal and sinus congestion often associated with acute and chronic sinusitis, allergic rhinitis, vasomotor rhinitis, influenza, and the common cold.

ADVERSE REACTIONS: Epigastric distress, drowsiness, dizziness, insomnia and nervousness.

PRECAUTIONS: Instruct patients not to drive or operate machinery if drowsiness occurs. Use with caution in patients with thyroid disease, heart disease, hypertension, diabetes or kidney disease. Excessive dosage or prolonged use may cause kidney damage.

DOSAGE: Adults — 2 tablets every 4 hours.
Children (6-12 years) — ½ the adult dose.

Each tablet contains 150 mg. acetaminophen, 150 mg. phenacetin, 25 mg. phenylpropanolamine HCl, and 22 mg. phenyltoloxamine citrate.

Source of Symptomatic Relief

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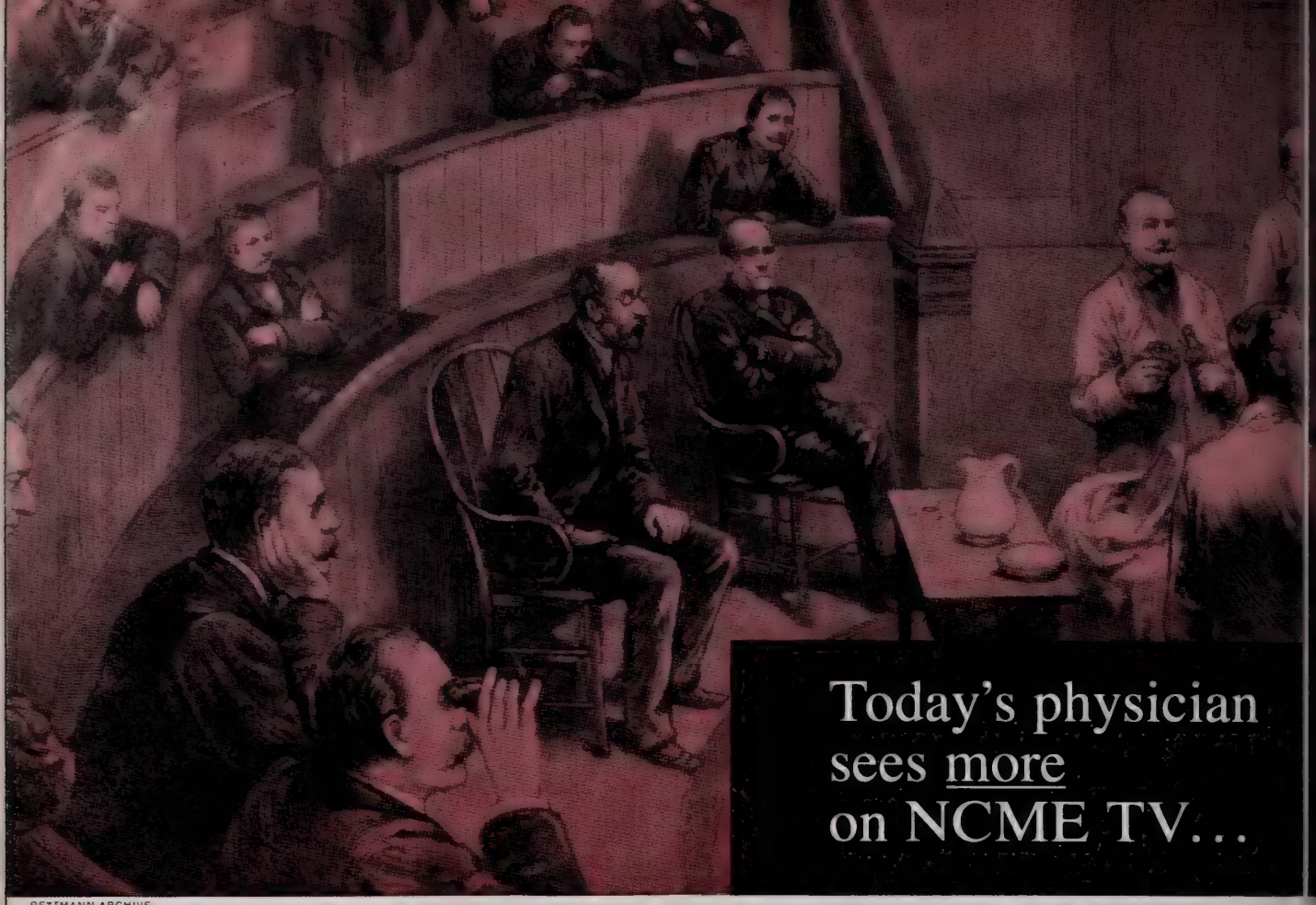
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That's nonsense, of course. But it's no more nonsensical than what some people say about aspirin. Namely: since all aspirin is at least supposed to come up to certain required standards, then all aspirin tablets must be alike.

Bayer's standards are far more demanding. In fact, there are at least *nine specific differences* involving purity, potency and speed of tablet disintegration. These Bayer® standards result in significant product benefits including gentleness to the stomach, and product stability that enables Bayer tablets to *stay* strong and gentle until they are taken.

So next time you hear someone say that all aspirin tablets are alike, you can say, with confidence, that it just isn't so.

You might also say that all registered nurses aren't alike, either.



Meet the President



O. L. N. Nelson, M.D.

President

Minnesota State Medical Association

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St. Paul
Photographer of executives and professional men.

See the President's Letter, Page 1321.

My Political Creed

I am a free citizen in a free nation.

Whoever diminishes my freedom as an individual diminishes the sum total of freedom in my country.

I am also a physician, free thus far to treat my patients to the best of my ability.

Abridge that freedom and the health of my patients is adversely affected.

These things being true, I cannot -- I will not -- stand idly by when these hard-won freedoms are under attack.

For I believe that the values upon which this country was founded are immutable and have not been eroded by the passage of years.

I believe that I, as a free citizen in a free land, am obligated to defend my beliefs in the ways permitted to me, and required of me, by our form of government.

Therefore, let no man seek to bar me from the political process; for it would be akin to denying my right to participate in the process that determines free government.



President's Letter

YEARS AGO AN unknown writer described four sorts of readers: "Sponges which attract all without distinguishing; Howre-glasses which receive and powre out as fast; Bagges which only retain the dregges of the spices and let the wine escape, and Sives which retaine the best onely."

Once again we are in an election year—this time the quadrennial extravaganza of presidential selection. Now, if ever, physicians must rise to the challenge to make the next Congress aware of and responsive to the problems and needs of American medicine. Already, more than a thousand medically-oriented bills have been introduced into the Congress. As enunciated by Carlyle, "Our duty is not to see what lies dimly at a distance, but to do what lies clearly at hand."

What, then, can we do? Of course, each of us must himself vote for the candidates of his choice. We must wield our not inconsiderable (and underrated) influence in the area of politics ("the affairs or activities of those who are engaged in controlling or seeking to control a government or its offices or departments"). We must contribute time wrung from our busy hours and moneys to support inescapably expensive campaigns.

Special note might here be made regarding the American Medical Political Action Committee (AMPAC) and our state component organization, the Minnesota Medical Political Action Committee (MINNPAC). Lest this latter designation be unfamiliar, let me remind you that it is the successor to NUHOPE, which Dr. James Blake founded and shepherded so well for so many years. The newly-named unit is under the experienced and enthusiastic direction of Dr. Richard Engwall. He would welcome your support, be it in time or moneys or both.

Sir William Osler has stated, "By far the most dangerous foe we have to fight is apathy—indifference from whatever cause, not from lack of knowledge, but from carelessness, from absorption in other pursuits, from a contempt bred of self-satisfaction." He said further, "The word of action is stronger than the word of speech."

May you readers be "Sives."

O. L. N. Nelson, M.D.,
President
Minnesota State Medical Association

STATE MEDICAL ASSOCIATION

minnesota medicine

Volume 51

Number 10

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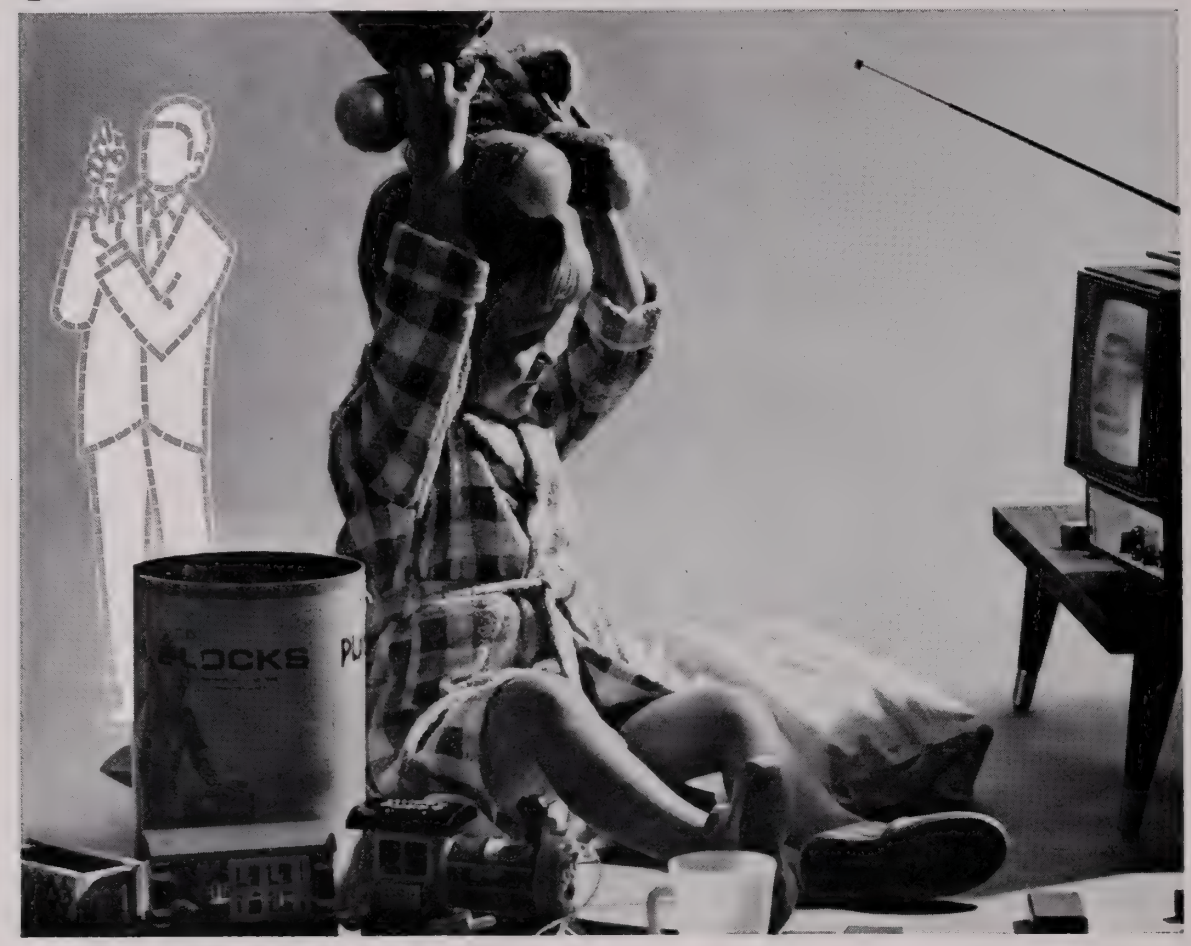
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See package literature for detailed dosage instructions for prophylaxis of streptococcus infections, surgery, gonorrhea, and severe infections.

How Supplied: Tablets V-Cillin K® (Potassium Phenoxymethyl Penicillin Tablets, U.S.P.), 125 mg. (200,000 units), 250 mg. (400,000 units), and 500 mg. (800,000 units).

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Adenomammectomy

Origin and Technique

CARL O. RICE, M.D.
Minneapolis, Minnesota

THE TERM "ADENOMAMMECTOMY" was first described in 1951.[1] It was derived from the Greek prefix "adeno" denoting a gland, the Latin "mamma" for breast, and the Greek "ektome" meaning excision of. Perhaps adenomastectomy would have been etymologically more correct, being then all of Greek derivation. But for a procedure designed to preserve cosmetic contour, adenomammectomy seemed linguistically softer and more euphonious.

A radiating incision for breast biopsy of a benign lesion is inadequate because it does not allow an opportunity to visualize any other portion of the breast than that which can be seen in the depth of the incision. The finger or instrument that has removed the lesion has done scarcely more than a grubbing procedure. It is a dangerous incision for the biopsy of a malignant lesion because the mechanical trauma that is inflicted in the vicinity of carcinomatous tissue may tend to disseminate the lesion rather than confine it.

An elliptical excision for biopsy, though somewhat neater surgically, has the same disadvantages as the radiating incision; in addition it will have contributed unnecessarily to disfigurement of the breast contour if the lesion is found to be benign. For a malignant lesion, if the biopsy is truly excisional, it will have served its purpose as an initial step toward radical mastectomy.[2]

Simple mastectomy for a benign lesion is mutilating, irretrievable and wholly unnecessary; for a malignant lesion it is inadequate except as a temporizing procedure; and it can never be considered a cure for cancer.

Surmounting the Pitfalls

Early in the development of this procedure a number of undesirable sequelae were encountered which, as they were obviated, made it possible to improve the technique as well as the end result. In order that these pitfalls might be avoided by other surgeons they are detailed in the following paragraphs.

Posterior Excision of a Lesion

In 1949 a mammary thoracic fold incision was being used[1] for the purpose of excising suspected benign tumors within the breast substance. In this procedure the breast was separated from the pectoral fascia to the point at which the lesion had been palpated, and the specific mass was then elliptically excised from the posterior surface of the breast.

During this operation multiple cysts or other lesions not palpated on clinical examination were almost universally encountered. This led to more extensive excision of breast substance from the posterior surface in an effort to eliminate the development of subsequent clinically palpable cysts which would require still another operation. Furthermore, if only the clinically palpable mass was removed and the uninvolved breast substance allowed to remain, the contour of the breast was not as smooth as seemed desirable because the excised tissue left a palpable crevasse covered with skin.

Allowing irregular masses of uninvolved breast substance to remain produced undesirable irregularities of contour.

Partial Adenomastectomy

A more extensive partial adenomastectomy was instituted in 1950; but because a portion of breast substance was left at the upper limit, (See inset, Figure 1) the remaining 1-cm ridge of breast tissue left the patient with a palpable cleft at the upper margin of the brassiere line. This too seemed undesirable as it often perplexed the patient who could palpate the ridge and presumed that it was tumor tissue that had not been completely removed.

Subcutaneous Mastectomy

Removal of all of the breast substance and an extension of the dissection of the gland into the subcutaneous fat was then done; but when this flap of redundant skin and subcutaneous tissue healed to the pectoral fascia, even though enough breast skin and subcutaneous adipose tissue remained to produce a redundant overhang, the cosmetic appearance was puckered and unsightly, leaving an uneven plowed look to the surface of the breast, with the overhanging redundancy constituting nothing more than a purse-like flap of skin.

Dissecting through the subcutaneous fat

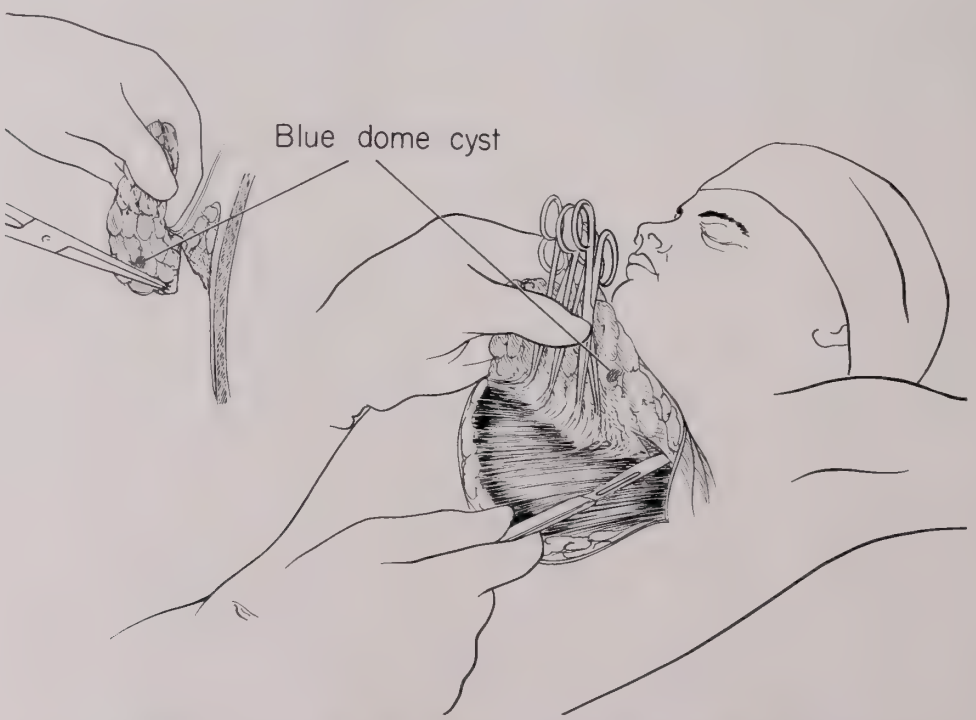


Fig. 1—Through a curved mammary thoracic fold incision the dissection off the pectoral fascia has been made to the upper limits of the breast substance. The row of Ochsner forceps at the upper margin of the everted breast substance has been placed and the incision has been started through the gland (see inset).

sometimes left a compromised circulation to the overlying skin, occasionally resulting in small areas of necrosis.

Endeavoring to eliminate the overhanging flap by excising an ellipse of skin from the apparent abundance of skin lying between the nipple and the mammary thoracic fold left the patient with a nipple turned underneath and no improvement in the contour.

Subtotal Adenomammectomy

Realizing that there is a layer of areolar elastic tissue between the breast substance and the subcutaneous fat, our next design was to leave a two-millimeter layer of "breast capsule" in the hope that the contour could be preserved. This did prove to be the case and resulted in adenomammectomy as shall be described in detail in the following paragraphs.

In 1950 the term adenomammectomy was adopted and with this procedure we have continued to remain content.

The Technique of Adenomammectomy

Lest the surgeon become discouraged while in the process of learning the pitfalls that have been encountered in the development of this procedure, the details of the technique are here described minutely.

The Incision

The curved incision is made directly in the mammary thoracic fold with a sharp scalpel and should be generous enough so that when the breast substance has been dissected off the pectoral muscle, the entire glandular area of the breast can be everted* and exposed to direct vision and palpation.

Healing of this mammary thoracic fold incision leaves an invisible scar after six months, whereas a differently placed incision either above or below, though not a serious objection, does leave a more visible scar. One of the dictums in plastic surgery is that of placing the incision in the normal folds of the skin.

Only when the findings indicate that a radical mastectomy is the most likely procedure, is a somewhat higher-positioned incision made, so as to be able to take advantage of the additional skin available at that point and allow closure of the elliptical defect which has been left after radical mastectomy has been performed.

*See Test Your Word Score Page 1367.

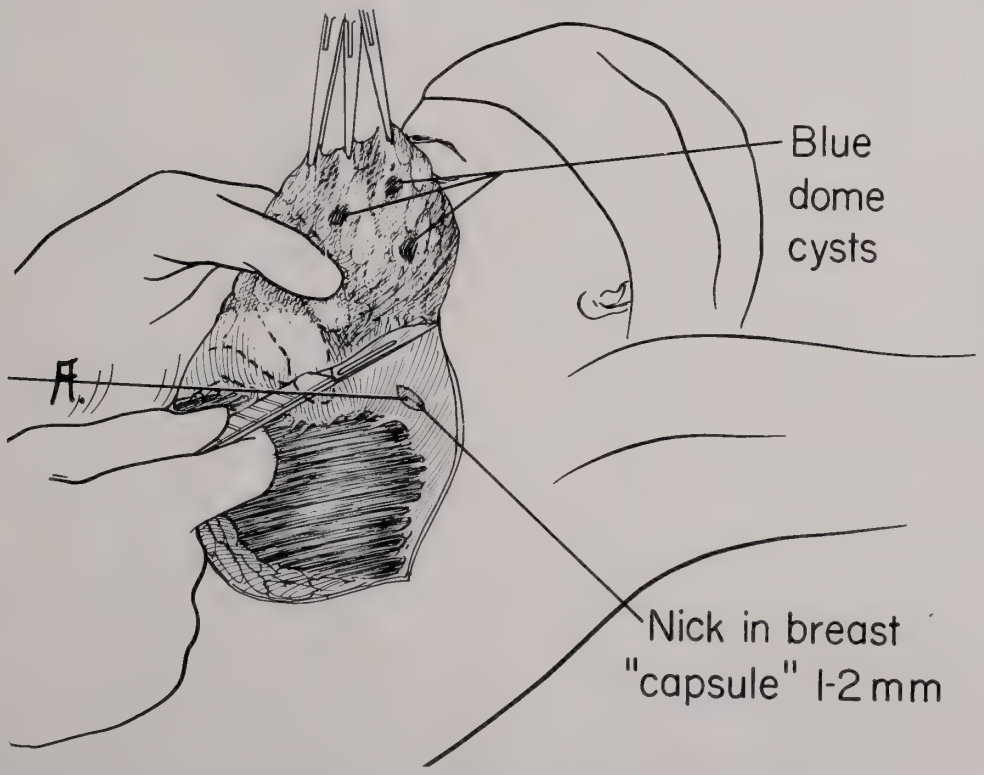


Fig. 2—The dissection of the breast substance from the breast flap has progressed and a niche in the breast capsule has been made to identify the depth of the capsule.

Dissection from the Pectoral Fascia

The skin incision extends directly to the areolar plane between the breast substance and the pectoral fascia lying upon the pectoral muscle. In this plane of cleavage the dissection is continued cephalad to the upper limits of the breast substance. This is best accomplished by holding the breast in the palm of the left hand as the surgeon palpates the upper margin of the breast substance between his fingers, lying upon the skin surface, and his thumb, placed against the under surface of the breast (Figure 2).

This dissection is made with the endotherm knife which, as it progresses through the areolar plane between the breast substance and the pectoral fascia, cauterizes the major portion of the small vessels and eliminates a considerable quantum of the bleeding. Other vessels are meticulously clamped with narrow pointed Rankin clamps. These bleeding points are coagulated with pinpoint precision by the endotherm in order to diminish, as much as possible, the burned tissue.

Turning the Breast Inside Out

It is now possible for the surgeon to evert the breast in order to visualize and palpate any portion of the breast substance from its back side, often revealing blue dome cysts or dilated ducts which were not clinically palpable before. Fibrous plaques or discrete tumors are easily felt between the palpating fingers and the thumb.

At this point in the procedure all of the breast substance which is to be removed now lies in the palm of the left hand along with its overlying skin and subcutaneous fat. The rounded contour of the breast is turned inside out, and the dissection of the breast substance, leaving a thin capsule, follows the rounded hemisphere of the everted breast (Figure 3).

Placement of Forceps on Breast Substance

A row of four or five Ochsner forceps is placed along the upper margin of the everted breast substance (Figure 1) with their handles matched to facilitate their wielding. They are held in the surgeon's palm along with the everted breast; and gentle tension is exerted upon this row of forceps everting the breast substance as it is being dissected.

Excising the Breast Substance

An incision is then made, with a sharp scalpel, through the upper margin of the breast substance (Figure 1 inset). As the subcutaneously situated "breast capsule" is encountered, the meticulous shaving of the breast substance follows as closely as possible the rounded and everted "breast capsule."

One or two millimeters of breast capsule must be allowed to remain with the subcutaneous fat. The stereognostic palpating fingers which are everting the breast substance are the guide to this point of excision. If the surgeon cannot be certain with regard to the depth of the remaining "breast capsule" he may make a small niche through it until the larger lobulations of subcutaneous fat identify the depth of the capsule.

The dissection continues distally along the everted curve of the breast as the row of Ochs-



Fig. 3—The line of dissection of the breast from the pectoral fascia is indicated by the arrow, and the curved portion of the arrow indicates the dissection of the breast substance from the breast flap—leaving a 2-millimeter layer of breast capsule.

ner forceps is placed on tension so as to keep the breast substance constantly everted for clear visualization of the dissection as it progresses (Figures 2 and 3). There is no blind dissection at any point.

The endotherm knife is not used for this dissection of the breast capsule lest it inadvertently penetrate too close to the under surface of the adjacent skin, thereby causing a burn, with areas of subsequent necrosis.

Bleeding points are meticulously clamped with sharp-pointed Kelly or Rankin forceps.

In the process of progressing distally from above, one encounters the areola and nipple area, carefully cutting across the collecting ducts, but fastidiously avoiding the nipple itself, lest damage to the nipple cause impairment of its circulation and subsequent necrosis.

Having passed the lower border of the areola the dissection is almost completed but is continued in the same manner to the margin of the incision.

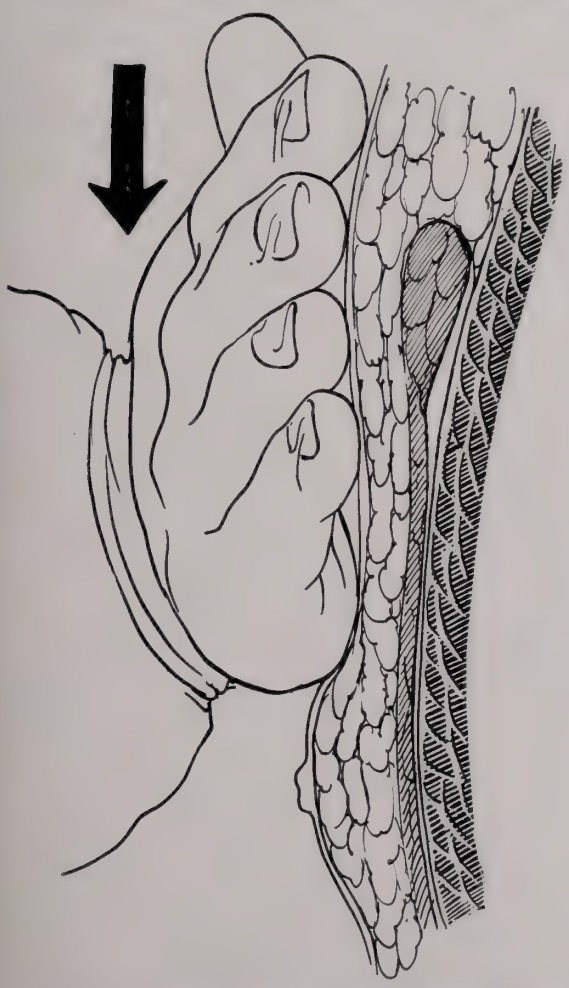


Fig. 4—The moist, palpating, gloved hand is passed from above downward over the breast flap to identify any irregularities that might require additional removal as demonstrated in Figure 5.

Controlling the Bleeding

The glandular substance of the breast has now been removed and a one-millimeter layer of breast capsule has been allowed to remain along with the subcutaneous fat, for cosmetic restoration: a very important detail of this operation.

During the dissection of the breast gland all bleeding points of any consequence are clamped with a Kelly forceps and subsequently cauterized with the point of the endotherm blade. However, one must avoid ironing the cut surface with the coagulating blade as this increases the area of burned tissue and consequently the postoperative exudate. This coagulation of the pinpoint bleeders must be done meticulously almost to the point of ennui. Caution with regard to the heat of the coagulator must be observed lest the heat penetrate and burn the under surface of the skin, to cause subsequent necrosis. The cut surface of the breast capsule must be absolutely dry. Warm packs, Gelusil, coagulating sponges, pressure, all contribute their bit; but the time consumed in waiting for the coagulating effects of these mechanisms is no greater than that expended in using meticulous pinpoint cautery with the endotherm. No further portion of the operation must be carried out until this control of the minute bleeding points has been completed. To allow *any* bleeding to remain defeats the primary adherence of breast substance to the pectoral fascia and will cause the breast flap to float upon the fascia in a pool of bloody exudate.

Re-evaluation of the Removed Breast Substance

In order to evaluate the removal of the proper amount of breast substance and the uniformity of its removal, the breast flap, after having been throughly controlled of its minor bleeding, is replaced on the chest wall. The moist palpating gloved hand is then passed from above downward over the breast flap. Any irregularities, ridges, or excessive amounts of breast capsule are readily palpated with the flat, moist, gloved hand (Figure 4). Palpating with a dry, bloody or sticky rubber glove or with the fingertips will not allow for accurate

interpretation.

The most commonly encountered irregularity is a small cleft of breast substance that has been left behind at the upper margin where the excision of the breast substance was started (Figures 1 and 5 inset). This and other irregularities produced by leaving an excessively thick portion of breast capsule can be removed with a curved shears until the palpating moist hand reveals a smooth contour from top to bottom (Figure 4). The remaining breast capsule should be uniformly two millimeters thick.

After these excessive and unevenly removed portions of breast capsule have been properly removed and the contour is smooth, minor bleeding points are re-evaluated, searched for and cauterized. No ties of any kind are used to control the bleeding points. To use ties produces more exudate than is produced by the meticulous pinpoint cautery.

Closing the Incision

Only after the field of excision is completely dry, two large, non-collapsible catheters are placed under the breast flap and brought out through a tight stab wound one inch below the lateral portion of the excision. These are anchored and held in position with a Japanese finger cot stitch and the catheters attached to continuous suction so as to keep the small amount of exudate from accumulating under the breast flap.

The two catheters are attached to a Y and then to active suction, which keeps the breast flap adherent to the pectoral fascia and eliminates the accumulation of small amounts of exudate which, if allowed to accumulate, will prevent primary healing of the raw surface to the pectoral fascia.

The skin is then closed with interrupted everting stitches of dermal and interspersed clips.

The Dressing

A one-strip Telfa dressing is placed across the line of incision, but no strapping of any kind is allowed across the breast in any area, as the pressure of a strapping will cause a ridge as the healing tissues adhere to one another.

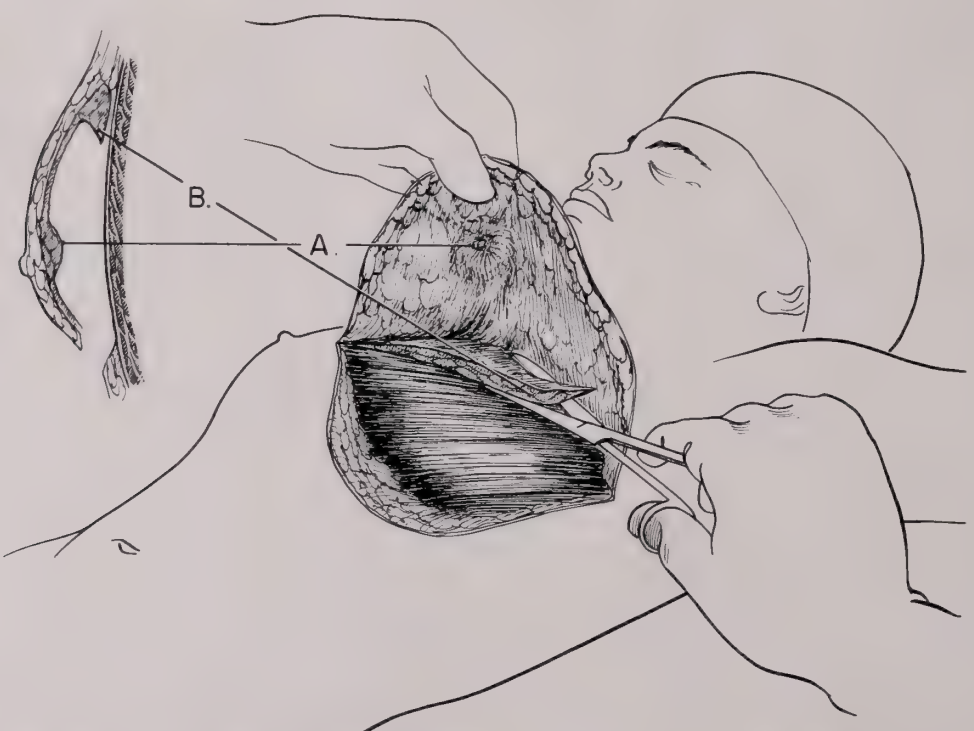


Fig. 5—Clipping away irregularities produced by leaving an excessively thick portion of breast capsule at any point is demonstrated (A and B). The remaining capsule must be uniformly 2-3 millimeters in thickness. Palpating the breast flap as demonstrated in Figure 4 will reveal these irregularities. All of the subcutaneous fat and the "breast capsule" remains with the breast flap. The skin edges are approximated with interrupted stitches and interspersed clips. No subcutaneous or other sutures are used.

Fashioning the Contour of the Breast

After the operation is completed and the dressings applied, the patient is placed in a semi-upright position so as to allow the normal redundant sag of the breast over the line of incision. If the operation has been meticulously done this positioning of the breast allows it to heal and develop a normal contour somewhat smaller than the contralateral breast, but in no instance a flat, male-type contour.

If there has been an inadvertent removal of the breast capsule over a small area, no attempt is made to re-approximate these edges of the capsule, as to do so will only add to the irregularity of the healing. If large plaques of breast capsule have been inadvertently removed, the breast contour will be distorted at that point.

No refashioning of the nipple or the areola is carried out, as this area will assume its normal position if the operation has been properly performed.

In the event of an inverted nipple existing prior to the operation, this can be corrected by taking a purse-string suture around the nipple from the outside, holding the nipple in the everted position.

Conclusions

Adenomammectomy is a completely satisfactory procedure for all breast biopsies.

Adenomammectomy provides a cure for fibrocystic disease, duct ectasia, fibrous plaques, and mastodynia from fibrous or cystic mastitis.

Adenomammectomy leaves a normal breast contour, though a somewhat smaller one.

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1. Rice, Carl O. and Strickler, J. H.: Adenomammectomy for Benign and Breast Lesions. Surg Gynec Obstet 93:759, 1951.

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Too Tough To Die

Cowboys sat tall and were too tough to die. At least so it would seem, judging from the memoirs of doctors who practiced among the ranches of the Old West. Take the eastern Oregon bunch grasser named Bill, whose horse kicked him in the forehead, right beneath his shaggy hairline. The hoof stripped a three-inch piece of scalp clean from the skull all the way from his forehead to the back of his head.

Bill tied the strip of flesh back in place with a red bandanna and rode 18 miles through sub-freezing weather to Farewell Bend. Blood ran down over his eyes and froze in cakes on his face. He strode into Dr. Urling Coe's house.

"Sew up this goddam fool head o' mine, Doc," he drawled, "'fore all them damn little brains o' mine falls out."

Dr. Coe cleaned and shaved the cowpuncher's head and put in 30 stitches while the cowboy laughed, joked and told tall tales. By the time he had finished, the temperature outside had fallen to near zero. Doc thought maybe his patient might want to bed down for the night; instead he saddled up and rode 45 miles to a ranch where he had promised to help out with the roundup.*

*Richard Dunlop: Doctors of the American Frontier, 1965.

Learning has come into the world not merely to clear men's eyes and give them mastery over nature and human circumstances, but also to keep them young, never staled, always new like the stars and the hills and the sea and the vagrant winds, which make nothing of times or occasions but live always in serene freedom from any touch of decay, the courses of their being some high law which we cannot disturb.—Woodrow Wilson.

Nobel Prize Winners In Medicine and Physiology

Niels Ryberg Finsen 1903

In recognition of his contribution to the treatment of diseases, especially lupus vulgaris, with concentrated light rays, whereby he has opened a new avenue to medical science.

"Thanks to the work of Downes and Blunt, of Duclaux, Arloing, Roux, etc., it is at present (1897) well established that light possesses an energetic bactericidal power. Thus everything argues, at least theoretically, in favor of the use of light in the treatment of superficial cutaneous diseases caused by bacterial infection, and yet this therapeutic procedure has remained unused to this day.

"Consequently I have thought it my duty to reundertake the study of this important question from top to bottom.

"As light only exerts its bactericidal effects very slowly, it is necessary to concentrate it by means of mirrors or lenses, at the same time excluding the heat rays of the spectrum, because when concentrated they cause burning of tissues."

Finsen then designed and constructed an apparatus that would concentrate light and at the same time reduce or eliminate heat, the main feature of which was a hollow planoconvex lens containing an ammoniacal solution of copper sulfate.

"I have employed the method of treatment by concentrated chemical rays in different infectious skin diseases, but above all in lupus vulgaris, an affection which presents particularly favorable conditions for putting this therapeutic procedure to work. It is known that lupus vulgaris is caused by the tubercle bacillus, that it is a local and quite superficial malady. On the other hand it is well established that light is capable of killing the tubercle bacillus.

"When a plaque of lupus has been subjected for a long enough time to the action of concentrated chemical rays, its margins, previously elevated, become smooth, the redness progressively diminishes, the skin regains its normal color, and ulcerations, when they exist, are cicatrized."*

*With acknowledgements to Theodore Sourkes: Nobel Prize Winners in Medicine and Physiology, 1966.

His Nganga* Failed

Raymond†, a Makorekore aged twenty years, admitted with pains in his abdomen and joints. He consulted a nganga in November 1959, who said he was bewitched by poison which had been added to his meat. The nganga treated him by applying his mouth to various parts of Raymond's body to 'suck' out the evil. He felt a little better after this. But as the pains returned, in June 1960, he consulted another nganga. This doctor also said that he was being harmed by a witch and told him that she was the wife of his sister's brother-in-law. Raymond could think of no reason for her enmity. The nganga made incisions over the patient's chest and back. He improved only slightly after this treatment.‡

*Nganga—Southern Rhodesian witch doctor.

†Raymond was admitted to a Southern Rhodesian hospital after his nganga failed to cure him.

‡Michael Gelfand: Witch Doctor, 1965.

Early Diabetes Mellitus

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WE NEED A guide to the early phases of diabetes mellitus, primarily because there are advantages in early diagnosis. Detection programs are based on this assumption. Discovery of diabetes before its "clinical" or "symptomatic" or "overt" phase might be especially advantageous. Herein lies our best hope of learning to prevent symptomatic diabetes mellitus and of assessing the benefits of therapy during the "pre-diabetic" period, prophylactic use of diet, oral hypoglycemia agents, etc.

Classification

There is a confusing variety of terms for the earliest phases of diabetes mellitus. One arbitrary classification is as follows:[1]

Phase 1:

"Pre-diabetes". In this group the pre-diabetic state starts at birth and lasts up to phase two. Pre-diabetes might be defined to include all diabetes suspects.

Phase 2:

"Sub-clinical diabetes" includes patients who occasionally can be shown on glucose tolerance tests to have diabetes, usually under stress (such as pregnancy). During sub-clinical diabetes, the stress which brings out the weakness may be a cortisone glucose tolerance test (while the patient still has a normal conventional glucose tolerance test).

Phase 3:

"Latent (asymptomatic) diabetes" is the period during which oral or intravenous glucose tolerance tests are abnormal. The patient may have a normal fasting blood sugar and no symptoms. This is sometimes called "chemical diabetes."

Phase 4:

"Clinical", "Symptomatic" or "Overt" diabetes. The 2,400,000 known diabetics in this country have reached phase 4, and have "clinical," "overt," "symptomatic" or "frank" diabetes.

The progression of diabetes is from phase

*From Diabetes Detection and Education Center; 916 East 15th Street.

The author is indebted to Gordon W. Wittich, B.S. in Pharmacy, Chief of Pharmacy, Mt. Sinai Hospital, for his cooperation in compiling the table.

one to two to three to four; this may be rapid or slow. Regression may occur from any of the four phases to the one preceding.

Chemical Signposts

A number of chemical signposts indicates that in the pre-diabetic phase metabolism is already abnormal. Based on these preliminary observations we should eventually have tests to diagnose patients in the pre-diabetic period (phase 1):

Pre-diabetics

1. In a group of pre-diabetics, the mean blood sugars of many glucose tolerance tests were shown to be above the means of the normals.[2]
2. "Immuno-reactive insulin" is higher in pre-diabetics 60 minutes after intravenous injection of glucose than in normals.[3]
3. Insulin-like activity is higher in the fasting state in pre-diabetics than in normals.[4]
4. Pre-diabetics show delayed use of insulin and insulin complexes.[5] This may account for the "hypoglycemic tail" which characterizes their glucose tolerance tests.
5. Free fatty acids are elevated within ten minutes after rapid glucose injection in pre-diabetics.[6] Return of free fatty acid levels to normal is delayed.
6. Synalbumen insulin antagonism is abnormally high in pre-diabetics.

Sub-clinical Diabetics

In contrast, there have been studies of so-called diabetes of pregnancy (phase 2); between pregnancies such patients should show the pre-diabetic picture just described. However, between pregnancies, patients with abnormal glucose tolerance tests during pregnancy may show no difference from normal populations in blood non-esterified-fatty-acid values; in glucose tolerance tests; in free fatty-acid responses, or in quantitative measure of growth hormone. The last observation argues against the school of thought that an elevation of growth hormone levels produces the abnormality in phases one, two or three. Something is going on, though it is not yet possible to test a patient during phase one, and often phase two, and pin a label on him.

At the University of Michigan, there is an on-going study of 169 close relatives of diabetes patients and 100 controls,[7] who started with normal glucose tolerance tests 12 or 15 years ago. All were between 20 and 40 years of age. Cortisone glucose tolerance tests were done. At the beginning of the study only three of 100 controls had abnormal cortisone glucose tolerance tests, judged by two-hour levels of 140 mgm.% glucose or above. Of 169 relatives of diabetic patients, 53 (28%) initially had abnormal cortisone glucose tolerance tests (nine times as many as in the control group). After a 12-year followup of the 53 relatives of diabetic patients with positive cortisone glucose tolerance tests, 26% already were frank diabetics. The other 116, who had negative cortisone glucose tolerance tests initially, produced only five new diabetics (4%). Cortisone glucose tolerance tests apparently have some predictive value in a survey of close relatives of patients with diabetes mellitus.

Clinical Signs

At this point it seems impractical to test large groups of the population (even relatives of diabetes patients) with studies of free fatty acids, insulin-like activity, immuno-reactive insulin, cortisone glucose tolerance tests or growth hormone assays. We now have to suspect the earliest phases of diabetes on clinical grounds. This is a "statistical chance" sort of thing. Any clue picked up adds to the "statistical chance" that a patient has diabetes mellitus now, or will have in the future. It follows that the more alert physicians are to clinical clues of early diabetes, the better the chance of diagnosing pre-diabetes, sub-clinical diabetes and latent diabetes.

Genetic History

A knowledge of genetics helps. Family history alerts physicians to the possibility of early diabetes in a patient. The suspicion may reach 100% certainty (of "pre-diabetes") in the offspring of two diabetic parents, or the identical twin of a diabetic.

Dr. Schumacher points out that a random fasting blood sugar (true) above 90 is strongly suspicious.[8] The suspicion should not be shelved just because glucose tolerance is normal or fluctuates. This test (or the two-hour

post-prandial blood sugar) may be up one week and down the next. A year or two later the diagnosis of diabetes mellitus often becomes obvious.

Reactive hypoglycemia may mean mild diabetes. The "hypoglycemic tail" on a glucose tolerance test may be the first abnormality to be demonstrated.

Glycosuria of stress (as in pregnancy diabetes) should alert the physician. On the other hand, he should not be misled by normal lactosuria of late pregnancy. Postoperative glycosuria must not be dismissed as a stress phenomenon without investigation. Neither should it be explained away on the basis of IV glucose, which often is given during or after surgery. At average rates of administration, IV glucose (5%) should not produce glycosuria, if the renal threshold is normal.

Rapid Shifts in Refraction

The ophthalmologist may pick up a prediabetic patient. Rapid shifts in refraction often result from changes in blood glucose level. Any patient who needs to change his glasses every month should be checked for diabetes mellitus. Xanthomata* of the eyelids (or elsewhere) and hyperlipemia retinalis are associated with high blood fats often seen in early diabetes. Extra-ocular muscle palsies accompany diabetes; if such is the case, prognosis is good and muscle paralysis may disappear after one or two months of good therapy. If it does not, a neurologist and/or neurosurgeon should be consulted. Other cranial nerves are occasionally involved in an early diabetic neuritis. Deterioration of the eighth nerve, for example, may be the first sign of diabetes. The hearing deficit may be a "fatigue deafness;" with repeated testing, performance of the patient seems to get worse.

Visceral Neuropathy

Visceral neuritis occasionally is the first symptom of diabetes. Early impotence, gastrointestinal complaints (including nocturnal diarrhea) and atonic bladder should suggest a glucose tolerance test.

Peripheral Neuropathy

Peripheral neuritis in diabetes mellitus produces symptoms as varied as the functions of the peripheral nerves. Olson and Schumacher[9]

*See Test Your Word Score Page 1367.

Table I
HYPERGLYCEMIC EFFECT

Class of Drug	*Generic Name*	*Trade Name*
Steroids	Cortisone	Cortone Cortogen Cortone
	Hydrocortisone	Cortef Cortril
	Prednisone	Deltasone Deltra Meticorten
	Prednisolone	Deltra-Cortef Hydeltra Meticortelone Sterane
	Triamcinolone	Aristocort Kenacort
	Dexamethasone	Decadron Deronil Gammacorten Hexadrol
	Methylprednisolone	Medrol
	Fluprednisolone	Alphadrol
	Paramethasone	Haldrone
	Betamethasone	Celestone
	Fluorocortisone Acetate	Florinef Acetate
Female Sex Hormones Estrogens	Estrone	Menformon Theelin Wynestron
	Estrogenic Substance (mainly estrone)	Neo-Amniotin Urestrin
	Estradiol Benzoate	Progynon
	Estradiol Dipropionate	Ovocyclin
	Estradiol Valerate	Delestrogen
	Sodium Estrone Sulfate I.V.	Premarin I.V.
	Ethinyl Estradiol	Estinyl Lynoral
	Piperazine Estrone Sulfate	Sulestrex
Synthetic Estrogens	Diethylstilbestrol	Stilbestrol Stilbetin
	Dienestrol	Synestrol
	Methallenestril	Vallestril
	Chlortrianisene	Tace
	Diethylstilbestrol Diphosphate	Stilphostrol
Growth Hormones	Chorionic Gonadotropin	Antuitrin S. A.P.L.
Human Placental Lactogen	(HPL)	Follutein
Human Growth Hormone	(HGH)	Pregnyl
Diuretics Thiazides	Bendroflumethiazide	Naturetin
	Benzthiazide	Exna
	Chlorothiazide	Diuril
	Cyclothiazide	Anhydron
	Hydrochlorothiazide	Esidrex HydroDiuril Oretic
	Hydroflumethiazide	Saluron
	Methyclothiazide	Enduron
	Ploythiazide	Renese
	Trichlormethiazide	Metahydrin Naqua
	Furosemide	Lasix
	Quinethazone	Hydromox

have shown that where conduction time measurements have been done, diabetic neuritis may be accompanied by slowed nerve conduction. One useful by-product is that diabetic neuritis may affect plans for surgical approach to such things as disc disease accompanied by neuropathy.

Dermatitis

Dermatologists often contribute to early discovery of diabetes. The skin lesion need not be as typical as "necrobiosis lipoidica." Patients with psoriasis are often diabetics. The skin lesion called dermatitis gangrenosa (with blisters or bullae) may be an early sign of diabetes mellitus. Xanthomata have been mentioned. Depuytren's contracture is associated, in a high proportion of cases, with diabetes.

Heavy Babies

The obstetrician can help. Everyone knows that a history of heavy babies makes the mother suspect. Early diabetes should also be suspected in cases of intra-uterine death, hydramnios, toxemia, kidney complications, vascular accidents and congenital anomalies.

Premature Vascular Disease

Premature vascular degeneration may be a clinical clue. Early coronary disease, for example, should make one suspect diabetes mellitus. The rule often used is that a coronary in a patient under 50 (especially if female) suggests diabetes. Similarly, early peripheral vascular disease (especially small-vessel disease as opposed to the occlusion of a large vessel) may be an early clue. Just as discovery of diabetic neuritis might slow up the surgical approach to co-existing surgically correctable causes (such as disc), so discovery of diabetic peripheral vascular disease should temper the decision of the vascular surgeon.

Other Associated Diseases

A number of metabolic and endocrine diseases are known to be associated with diabetes. In some cases this seems to be merely a statistical thing; in others, the hormonal abnormality causes diabetes, or brings out a latent genetic tendency. Included in this list should be gout, acromegaly, hyperthyroidism (Graves[1] disease), hypercorticosteroidism (Cushing's syndrome and hyperaldosteronism), pheochromocytoma and hyperglucagonism.

Not to be ignored is the increasingly long list of hyperglycemic drugs and hormones currently prescribed. Patients discovered to have hyperglycemia after administration of these compounds should be considered pre-diabetics who have been "unmasked" by a relatively minor stress (Table 1).

If sufficient attention were paid to these clinical clues by all physicians, the result would be a most effective diabetes detection program. The diagnosis of early diabetes mellitus is a "statistical chance" sort of thing. Any clue picked up adds to the "statistical chance" that a given patient will prove to have diabetes now, or in the future. The search is worth the trouble. We have reached the point where treatment of early diabetes may postpone or prevent "symptomatic" or "overt" diabetes.

Autohemic Therapy

For many years one L. D. Rogers was the head and chief owner of the National Medical University of Chicago. The school was a low-grade institution, virtually a diploma mill. Rogers is a promoter of medical schemes and fancies. Like many other cultist leaders he is constantly founding societies of which he is the chief panjandrum. . . Finally, he got the notion called "autohemic therapy." "It consists," he says, "in giving the patient a solution made by attenuating, hemolizing, incubating and potentizing a few drops of his or her own blood, and administering it according to a refined technic developed by the author." . . He wrote a book called "Autohemic Therapy" and organized the Autohemic Practitioners. Newspaper publicity in the form of full-page advertisements and clever press agentry fetch the come-ons for the course. The appeal is made cleverly to the antimedical cultists of all varieties by the slogan "without use of bugs or drugs." A clever and shrewd old fakir is L. D. Rogers!*

*Morris Fishbein, M.D.: The New Medical Follies, 1927.

Early Detection and Control of Diabetes*

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THE FIRST STEP in fighting diabetes is finding the diabetic. According to the National Health Survey's most recent estimates, there are 2.8 million diagnosed and 1.6 million undiagnosed diabetics. Current studies indicate that these figures are conservative.

Screening

The process by which we find and identify suspected diabetics is called screening. Screening is the presumptive identification of unrecognized disease by a variety of rapidly applied testing procedures. In order to detect diabetes in its earliest stages, screening programs must be expanded and become more selective.

The superiority of blood testing over urine testing is beyond question. The blood test is not only more sensitive, but also far more specific. Using blood tests makes it possible to identify more diabetics while sending fewer false positives to already busy private physicians. Furthermore, improved laboratory analysis of blood glucose on the Auto Analyzer has increased the efficiency of our screening techniques: now 40 to 60 specimens per hour can be analyzed.

High Yield Groups

Why do we screen? Efficient epidemiological programs produce maximum results with a minimum investment of time, money, and effort. Furthermore, screening enables the practicing physician to best utilize his skills. He can concentrate on those most likely to need his professional services—those who are over forty, overweight, relatives of diabetics, and mothers who have given birth to babies weighing more than nine pounds.

These high-yield groups have, on experience, produced the largest proportion of diabetics.

*Presented at the dedication of Diabetes Detection & Education Center, Minneapolis, Minnesota, November 10, 1967.

†Chief of the Diabetes and Arthritis Control Program, National Center for Chronic Disease Control, Bureau of Disease Prevention and Environmental Control, Public Health Service, Department of Health, Education, and Welfare, Arlington, Virginia.

The most effective screening program must be concerned not only with looking for diabetes among these particular population groups, but also must see that positive screenees are brought to diagnosis (and treatment when necessary) and that physicians cooperate in reporting diagnosis results.

Approximately 800,000 Americans were blood-tested for diabetes last year.* Out of this number, only 7,700 new diabetics were discovered. This is a very disappointing figure when we consider that there are an estimated 1.6 million "hidden" diabetics. The figure is also disappointing when we consider the number of diabetics that *can* be discovered *if* we concentrate our efforts in those areas where diabetics are found in greatest numbers. There is not a screening program in the U.S. that could not double its yield of new cases with very little additional effort or expense by more thorough and sensitive screening techniques.

Today's problem is not just to find and treat diabetes, but to find and treat it as early as possible. Although we have no cure for diabetes, it can be easily controlled with diet, medication, and exercise. The disease can be better controlled if it is discovered early when the manifestations are minor and less injurious to health.

The best screening programs are those that are organized as joint efforts of local health departments, medical societies, and diabetes associations. Each of these groups offers specialized skills that the others cannot provide. A combination of these separate talents and skills should produce adequate leadership for any local epidemiological experiment.

Federal Employee Group

Our experience with the Federal Employee Screening Program has shown that periodic retesting of those who have had prior positive tests, but have not been diagnosed diabetic, will identify many new cases. Since July 1960, more than 50,000 federal employees have been screened in nine cities across the nation. Screenees are instructed to eat their usual breakfast and fast for two hours after reporting for work. At that time each person is given a 75 gm. carbohydrate cola drink (glucola). Venous blood specimens are drawn between one hour and 45 minutes and two hours and 15 minutes after the carbohydrate is taken.

For this program the screening level for positives is relatively low: 130 mg. per 100 ml. Tests are made on plasma which is easier to analyze than whole blood but gives higher readings. Direct referral is made to private physicians for diagnosis when the screening plasma value is 300 or more. When the screening level is between 130 and 299, glucose tolerance tests are administered by the health unit physicians.

In 1964, 10.9 percent tested positive and 2.1 percent were confirmed as new diabetics. This is the highest figure we have obtained since the study began. In 1965, 9.5 percent tested positive and 1.6 percent were confirmed new diabetics.

Suspects

Unfortunately, there are no adequate estimates of the number of persons in the U.S. who can be considered diabetes "suspects." Such estimates are not easy to obtain, and agreement on definitions and criteria is difficult to reach. But available data indicate that the number of diabetes suspects may be very large. Because we anticipate an exceptionally high yield from this group, their discovery should be of prime importance to any screening program.

Suspects are of two types: unsuccessful referrals and borderline cases. Unsuccessful referrals are those positive screenees who either failed to report to the doctor for diagnosis or were incorrectly diagnosed. Borderline cases have registered blood glucose levels just below the referral line. With a lower screening level, the latter group would have been referred to a physician for diagnosis.

The importance of suspects can be supported by some of our experiences with the Federal Employee Screening Program. In a special study, those who did not volunteer for retest were invited to have a glucose tolerance test. In a two-year period (1961-62), 18,690 federal employees were screened in the Washington area, yielding 1,922 positives and 259 new cases; 3,151 of those who originally tested negative volunteered for retesting. The yield from this group was 14.0 per thousand (almost

*As reported voluntarily to the United States Public Health Service: Some diabetes screening programs do not report.

as high as the total yield for the original group of screenees). Of the positive screenees who had not been diagnosed diabetic, 843 received either an additional screening test or a glucose tolerance test. In this group, 128 additional cases of diabetes were identified. Thus almost one in four of the persons with initial positive results was identified by a private physician as diabetic. Further testing of this suspect group gives us an unusual opportunity to test the preventive measures that we presently know about—particularly weight reduction and control—and to apply new research findings.

Elevated Blood Glucose with Negative Retest

Our considerable experience with diabetes screening programs has taught us that testing should be continuously provided for persons who have exhibited elevated blood glucose levels, even if the retest results have been negative and they have, therefore, not been referred to physicians (or were referred but received no diagnosis). The yield of new cases of diabetes among this group is exceedingly high even when a retest is done within two years of initial testing. We must not assume that a large proportion of those with positive screening results but no physician's diagnosis will voluntarily seek another test.

People Over Forty

In mass screening efforts, particular attention must be given to testing people over 40, as this is where we have found the largest proportion of new cases. Little can be accomplished by testing those under age 25. Even less significant results can be expected from testing those under 15 years of age (among children under 15, only one in 2,500 will have diabetes).

What can be done, then, to solve these multiple problems of finding the "hidden" diabetic? First of all, the practicing physician must cooperate fully with the screening program in the planning and evaluation stages. He must be the chief agent for diagnosis and followup (and continuing followup). His findings should be sent to the screening center to allow for the continual evaluation of the effectiveness of the screening program.

Disposition

At the screening program, screenees should be warned that the screening test is not a diagnosis, and that further tests and referral to a physician may be necessary. Positive screenees should be informed of their test results and scheduled for a retest appointment. Screenees should also be informed of retest results. Those who retest positive should be referred to a physician. Each referral letter to the physician should be accompanied by a form to be filled out and returned when diagnostic studies are completed.

The private practicing physician is the chief man on the diabetes control team. He sees those patients in his office who may not be reached by mass screening programs—especially those who are over forty, overweight, related to a diabetic, or women who have given birth to babies weighing more than nine pounds. The practicing physician must be on the lookout for the classical symptoms of diabetes: those who have spilled a little sugar during pregnancy or have unexplained neurological manifestations, frequent changes in visual acuity, slow wound healing, etc. Persons evidencing any of these characteristics should be blood-tested for diabetes once a year.

The physician must be prepared to inform all diabetes suspects of the nature and symptoms of the disease. He must instruct, or arrange instruction for the patient in diet, urine testing, insulin injection and measurement, syringe sterilization and other equipment maintenance, general body hygiene, and dental and foot care. The patient should also be warned of probable complications. The physician must join in the search for new methods and techniques of patient education, including programmed instruction, team-teaching, audio-visual aids, etc.

The physician should be acquainted with all available patient information and teaching resources (local diabetes associations, local medical societies, etc.). We cannot assume that because a patient has been instructed in the maintenance and care of his disease he is fully informed. Repetitive teaching is a must.

The private physician, then, assumes the responsibility of testing, diagnosing, prescribing,

counseling, and followup. He can be an even bigger help if he is on the lookout for signs of diabetes and tests accordingly in his own office. He must be on the alert for the high-risk groups. Then, and only then, will he be able to discover diabetes in its earliest stages when damage is slight and the chances for progression and complications are reduced. Only if every physician, in his office and in cooperation with health agencies, local diabetes associations, and medical societies, actively lends himself to diabetes screening and follow-up activities, will we be able to find the 1.6 million undiagnosed cases at large today.

Abdominal Migraine Syndrome

Various writers have classified as a syndrome the symptoms of abdominal pain, nausea, vomiting, and sometimes diarrhea that are frequently a conspicous part of the clinical picture of migraine (Brams, Blumenthal). The abdominal migraine syndrome is seen primarily in children or in adults who have had migraine for many years. Typical is a history of colic as a baby and a family history of headache or biliousness or both. Not infrequently the abdominal symptoms continue during childhood without attacks of headache, or may alternate in their occurrence with attacks of cephalalgia, or may continue after the headache has ceased. Parenteral administration of ergotamine usually causes prompt subsidence of symptoms. Desensitization with intravenous histamine affords more prolonged relief.

Durham, Robert H.—Encyclopedia of Medical Syndrome
Hoeber Medical Division, Harper and Row, New York

Shakespeare: on the Effects of Poison

"There is so hot a summer in my bosom,
That all my bowels crumble up to dust:
I am a scribbled form, drawn with a pen
Upon a parchment, and against this fire
Do I shrink up."

"How fares your majesty?"

"Poison'd, ill fare; dead, forsook, cast off:
And none of you will bid the winter come
To thrust his icy fingers in my maw,
Nor let my kingdom's rivers take their course
Through my burn'd bosom, nor entreat the north
To make his bleak winds kiss my parched lips
And comfort me with cold."

"O that there were some virtue in my tears
That might relieve you!"

"The salt in them is hot.
Within me is a hell; and there the poison
Is as a fiend confin'd to tyrannize
On unreprievable condemned blood.
The tackle of my heart is crack'd and burn'd,
And all the shrouds wherewith my life should sail
Are turned to one thread, one little hair;
My heart hath one poor string to stay it by."*

*King John to Prince Henry and Philip in King John V, 7.

Diabetic Angiopathy and Sulfonylurea Therapy*

MARIOS C. BALODIMOS, M.D.†
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THE INTRODUCTION OF INSULIN in the therapy of diabetes in 1922 has saved the lives of millions of persons and has increased considerably their life expectancy. The prolongation of life by insulin has resulted, however, in an increase in the frequency and extent of atherosclerosis and microangiopathy among patients who live for long periods with their disease. This increase has led to studies to elucidate the presumed deficiencies of insulin therapy or even to reveal its causative role for these complications. Neither has been accurately clarified. Very few clinicians blame exogenous insulin for deleterious effects, except for the hazard of hypoglycemia and its consequences. After 45 years the basic safety of insulin use remains undisputed.

The sulfonylurea compounds, introduced in 1955, have made treatment more convenient for many older patients; the number of those responsive to such therapy has been variously estimated as 25 to 40% of all diabetics. Furthermore, the safety record of these compounds has been satisfactory.

Morbidity and Mortality

It is now possible, after more than a decade of use of oral hypoglycemic agents, to appraise their effectiveness in preventing or postponing atherosclerosis and the specific microangiopathy of diabetes which are responsible for most of the morbidity and mortality of the disease. Sulfonylureas have been considered to possess not simply hypoglycemic, but also "antidiabetic" properties, because they promote the release of endogenous insulin. However, their record in protecting from complications has to

*Presented in part at a Symposium on diabetes held at the Diabetes Detection and Education Center, Minneapolis, November 11, 1967.

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†Elliott P. Joslin Research Laboratory, Department of Medicine, Harvard Medical School, the Diabetes Foundation, Inc., the Joslin Clinic and the New England Deaconess Hospital, Boston, Massachusetts.

We gratefully acknowledge the valuable technical and secretarial assistance of Mrs. Cele Dorris, Miss Theresa M. Smith, R.N., and Mrs. Mary C. Goltsos.

be compared with that of insulin therapy, in order to determine whether oral sulfonylurea therapy is superior to insulin, and also whether it is equal to or at least not inferior to insulin in postponing vascular complications.

Sulfonylureas have been used at the Joslin Clinic on several thousand diabetic patients.[1-4] In a series of clinical studies[5-8] we have attempted to answer the above questions.

Vascular Complications

Of a total of 125 patients who had taken tolbutamide for eight to 10 years continuously 101 were examined for the presence of diabetic angiopathy and these findings were compared "blindly" to those in suitable controls, i.e., 87 patients with "mild" diabetes who had never received oral sulfonylurea therapy and who had been treated either with small doses of insulin or with dietary restriction alone. It was found that angina pectoris or myocardial infarction, cerebral vascular accidents and peripheral vascular disease occurred with equal frequency in the tolbutamide-treated patients and in the controls[6] (Figure 1).

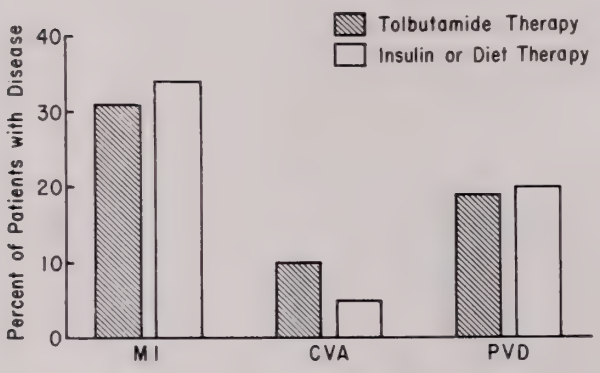


Fig. 1—Cardiovascular disease after eight to 10 years of tolbutamide therapy. MI = Angina or myocardial infarctions; CVA = Cerebral vascular accidents; and PVD = Peripheral vascular disease.

Diabetic Nephropathy

The clinical demonstration of diabetic nephropathy is difficult and unreliable. Indirect indices of renal function may be used. In this study[6] significant proteinuria was rare in both groups and blood urea nitrogen levels were no higher in the sulfonylurea group than in the controls.

Diabetic Retinopathy

Diabetic retinopathy, on the other hand, can be easily demonstrated by careful ophthalmoscopic examination, following dilatation of the pupils. We recorded and documented these changes by fundus photography both in patients treated with sulfonylureas and in controls treated with small doses of insulin or with diet alone. Retinopathy was found in 40% of the total of 152 patients. The relative frequency of retinopathy in those treated with sulfonylureas and in the controls was not significantly different.[8] Retinopathy in sulfonylurea-treated patients was found also by others[9,10] with similar or lower frequency compared to insulin-treated patients.

Although the frequency of retinopathy did not seem to be influenced by the form of antidiabetic therapy it was significantly dependent on the lack of "chemical" control of the metabolic abnormality. Irrespective of type of antidiabetic therapy, those who had maintained good control of diabetes (as determined by another observer independently and in a "blind" fashion) had a significantly lower frequency of diabetic retinopathy than those with only fair or poor control[8] (Figure 2). Reports of the majority of investigators who had studied the frequency of angiopathy in relation to the degree of control of diabetes are in agreement with the above findings: namely, that angiopathy is found more frequently among patients who have had an unsatisfactory control of diabetes over the years.[11]

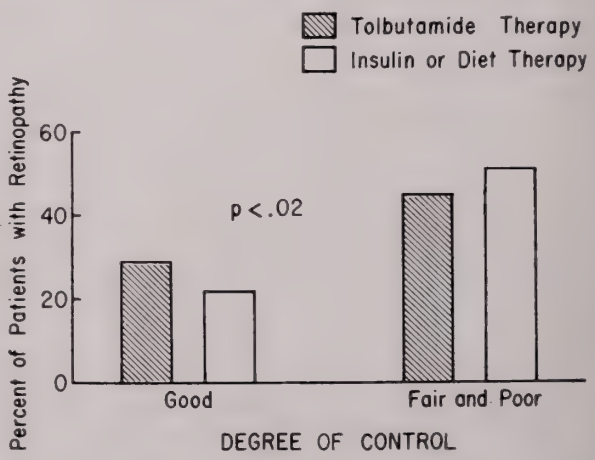


Fig. 2—Diabetic retinopathy in patients under various forms of therapy and different degrees of diabetic control.

Death and Pathologic Findings

The causes of death, as reported on death certificates, of all Joslin Clinic patients treated with sulfonylurea compounds for variable periods were compared with the causes of death of all patients of the Joslin Clinic, with onset of diabetes after 40 years of age, who died between 1956 and 1964[5] (Table 1). A remarkable similarity of causes of death is evident from this table between sulfonylurea-treated patients and total deaths at the Joslin Clinic, indicating again that there was no obvious shift in the morbidity on account of sulfonylurea therapy.

In a later study we compared, in a "blind", unbiased fashion, the autopsy findings of 55 patients who had received sulfonylurea therapy for an average of 46 months with those of suitable controls who had been treated with insulin or diet alone.[7] Pathologic evidence of myocardial infarction, diabetic nephropathy, diabetic retinopathy and cerebral vascular accidents was found with equal frequency in sulfonylurea-treated and control patients (Figure 3). The frequency of peripheral vascular disease as evidenced by gangrene and/or amputation of a lower extremity was actually greater in insulin-treated patients ($P < .05$). This was attributed to the customary use of insulin in diabetic patients with severe infection and gangrene.

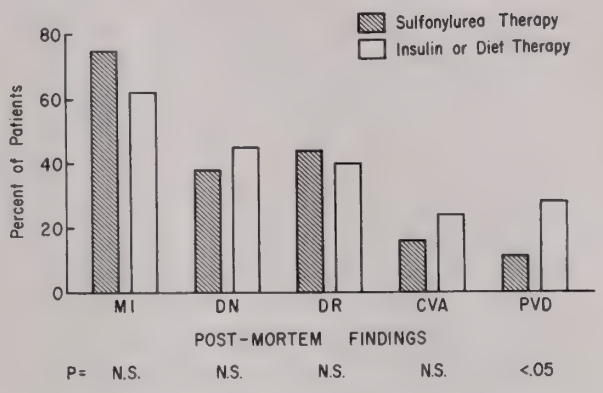


Fig. 3—Post-mortem findings after long-term sulfonylurea therapy. MI = myocardial infarcts; DN = diabetic nephropathy; DR = diabetic retinopathy; CVA = cerebral vascular accidents; and PVD = peripheral vascular disease.

Conclusions

The results of the studies referred to above[5-8] are reassuring. They include studies on large numbers of patients, both living and dead, treated for fairly long periods of time with sulfonylurea compounds, and compared to suitable controls. These studies have failed to show a higher frequency of cardiovascular, cerebral or peripheral vascular disease after oral therapy. Similarly, no differences were observed in the major clinical manifestations of diabetic microangiopathy, i.e., retinopathy and nephropathy.

On the other hand, no superiority of sulfonylurea over insulin therapy in the prevention of diabetic angiopathy was evident. Hence the results of this study suggest that one should not expect to achieve results superior to those obtained by insulin therapy, as was hoped initially after the introduction of oral agents. The factors responsible for the development of microangiopathy and for the accelerated

TABLE 1.
Causes of Death in Patients with Onset of Diabetes after Age 40*

Cause of death	All known deaths of diabetic patients. 1/1/1956-2/19/1964 No.	Percent	All patients who received sulfonylureas No.	Percent
Cardiovascular disease (incl. gangrene)	3146	(58%)	328	(60%)
Cerebral vascular disease	751	(14%)	77	(14%)
Renal disease	244	(5%)	28	(5%)
Total vascular deaths	4141	(77%)	433	(79%)
Cancer	631	(12%)	64	(12%)
Infections	268	(5%)	24	(4%)
All other causes	356	(6%)	29	(5%)
Total deaths	5396	(100%)	550	(100%)

*Experience of the Joslin Clinic. Data tabulated with the collaboration of the Statistical Bureau of the Metropolitan Life Insurance Company.

morbidity and mortality from atherosclerosis in diabetes mellitus, including severity of the underlying defect, etc., still remain elusive. Careful "chemical" control of the metabolic abnormality, by whatever means, gives the best results and is at present the best known guaranty for postponing and minimizing the vascular complications of diabetes.

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It takes a heap o'livin' in a house t'make it "home,"
A heap o' sun an' shadder; an' yer sometimes hev t' roam
Afore yer reely 'preciate the things ye lef' behin'
An' hunger for 'em somehow, with 'em allus on yer mind.
It don't make any differunce how rich yer git ter be,
How much yer chairs and tables cost, how great yer luxury.
It ain't "home" to yer, tho' it be the palast of a king,
Until, somehow, yer soul is sort o' wrapt 'round everything!—*Anon.*

Minnesota Medicine Cover Photographs

In order to encourage more physicians to submit color slides for use on the cover of MINNESOTA MEDICINE the competition is being discontinued. The picture editor now invites all physician-photographers to send 35 mm. color slides of suitable subjects for consideration as cover pictures. The format must be horizontal because of printing limitations. Pictures high-lighting Minnesota seasons, places, and activities will have an automatic advantage. No limit as to the number of slides sent will be set, but all slides should be individually identified. All slides will be returned. Physicians whose pictures are used as covers will be recognized in MINNESOTA MEDICINE. We can use many more pictures than we have received in the past.

Whipple's Disease*

Early Diagnosis

RICHARD BORNSTEIN, M.D.†
ATHANASIOS THEOLOGIDES, M.D., Ph.D.‡
B. J. KENNEDY, M.D.§
Minneapolis, Minnesota

WHIPPLE FIRST DESCRIBED the disease which bears his name in 1907.[1] The original report has been referred to as a "classic of clarity, objectivity and completeness."[2] All the outstanding features of this disease were recorded, including the presence of rod-shaped structures in a lymph node. However, the syndrome of migratory arthritis, diarrhea, abdominal cramps, progressive weight loss, cutaneous hyperpigmentation, and lymphadenopathy represents the more advanced and terminal stage of the disease.

Since Whipple's disease has been shown recently to be potentially curable with appropriate antibiotic therapy, it is advantageous to establish the diagnosis early. This is exemplified by a patient in whom the initial clinical diagnosis of lymphoma had previously been made. In failing to respond to cyclophosphamide therapy a re-evaluation of the illness established the diagnosis of Whipple's disease.

Case Report

History

This 59-year-old white male farmer was readmitted to the University of Minnesota Hospitals in August, 1967, complaining of weight loss, abdominal cramps, anorexia and diarrhea. The past medical history revealed 20 years of intermittent migratory arthritis involving predominantly the hands, wrists, and ankles, and two years of increased fatigue and weakness. In the fall of 1966 he noted intermittent constipation, occasional fever and night sweats, and a "lump" in the abdomen. Because of these symptoms he consulted his physician in April, 1967.

Examination

Physical examination revealed a left upper quadrant abdominal mass and axillary and inguinal lymphadenopathy. An anemia was treated with transfusions. An exploratory laparotomy revealed diffuse

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See editorial page 1359.



Fig. 1—Roentgenogram of upper gastrointestinal tract including part of small bowel, showing coarsening and thickening of the mucosal folds and dilation of the small intestine.

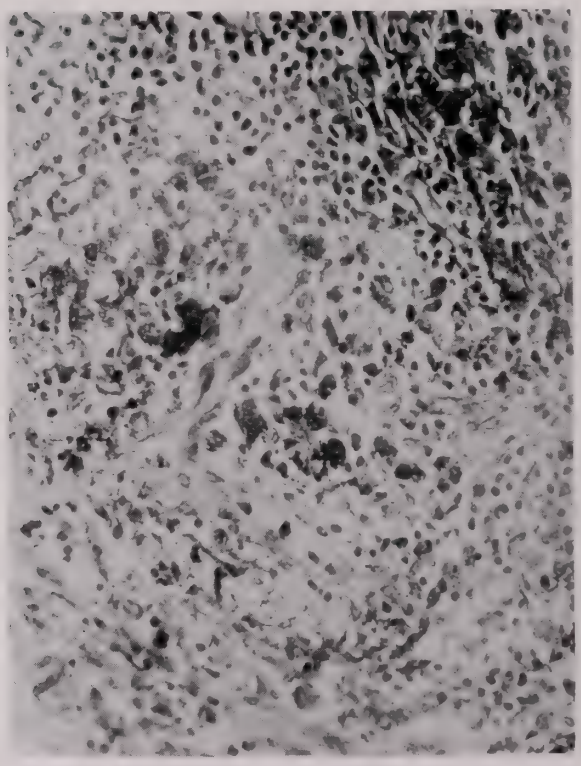


Fig. 2—Lymph node showing PAS positive particles (PAS stain × 250).

lymphadenopathy, and the histologic appearance suggested Hodgkin's disease. This material along with biopsies of the axillary and inguinal nodes was subsequently interpreted as probably benign adenitis.

He was referred to the University of Minnesota Medical Center in May, 1967, for further evaluation. Physical examination showed a pale, cachectic, chronically ill man. Small, firm lymph nodes were palpable in the cervical, axillary, and inguinal regions, and an ill-defined upper-quadrant abdominal mass was detected. Ulnar deviation of the wrists was noted.

Laboratory Studies

Laboratory studies revealed a hemoglobin of 11.4 g/100 ml., a sedimentation rate of 105 mm. at one hour, occult blood in the stool, serum albumin of 2.6 g/100 ml., and serum gamma globulin of 3.6 g/100 ml. with a diffuse peak in the electrophoretic pattern. An upper gastrointestinal radiographic examination was normal. A peroral small intestinal biopsy yielded insufficient material for study. The lymph node biopsies were interpreted again as non-specific inflammatory change. On clinical grounds it was decided to treat the disease as a lymphoma; a course of intravenous cyclophosphamide was given followed by maintenance oral administration for two months.

In August, 1967, the patient described watery diarrhea, abdominal cramps, anorexia, and further weight loss. An additional physical finding of hyperpigmentation of the exposed areas of the skin was noticed for the first time.

The hemoglobin was 8.6 g/100 ml., white blood cell count 4,800 mm^3, platelet count 403,000 mm^3, and sedimentation rate 112 mm. in one hour. Occult blood persisted in the stool. The fecal fat was increased at 18 g/day, and the serum carotene and vitamin A levels were decreased. An upper gastrointestinal x-ray series with small-bowel follow-through revealed coarsening and thickening of the mucosal folds and dilation of the small intestine, particularly of the distal duodenum and jejunum (Figure 1). Peristalsis also appeared sluggish, but passage of the contrast media was normal through the small bowel. A barium enema revealed occasional small diverticula. An axillary lymph node biopsy and a subsequent small intestinal mucosal biopsy were diagnostic of Whipple's disease (Figures 2-5).

The patient was given a 14-day course of procaine penicillin 600,000 units and streptomycin 0.5 g. intramuscularly twice a day. Marked improvement occurred by the end of the first week of treatment, consisting of increased appetite, weight gain, and a return of bowel function to normal. The patient was then begun on tetracycline, 250 mg., four times a day, to be continued for a period of ten to twelve months.

Discussion

Whipple's disease typically involves middle-aged white males and is clinically characterized by arthritis, hyperpigmentation of the skin, abdominal cramps, diarrhea, weight loss, fever,

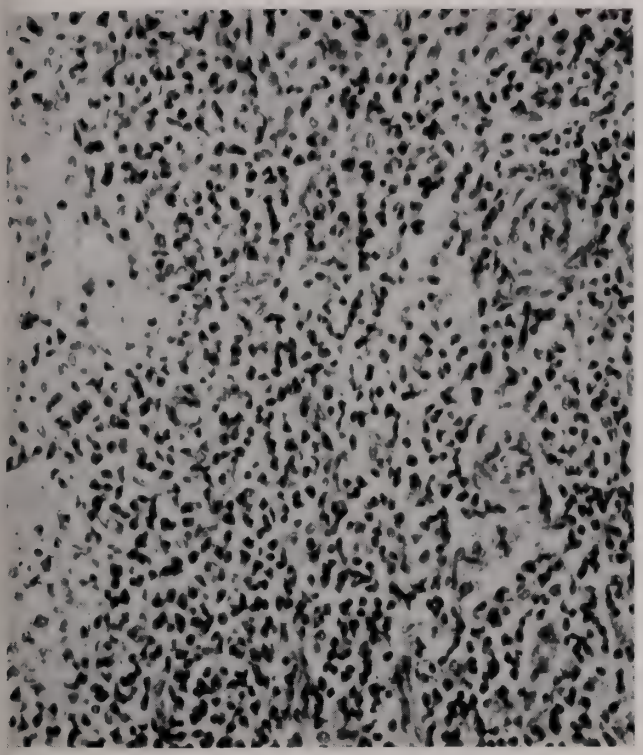


Fig. 3—Lymph node showing histiocytic infiltration (Hematoxylin and Eosin × 250).

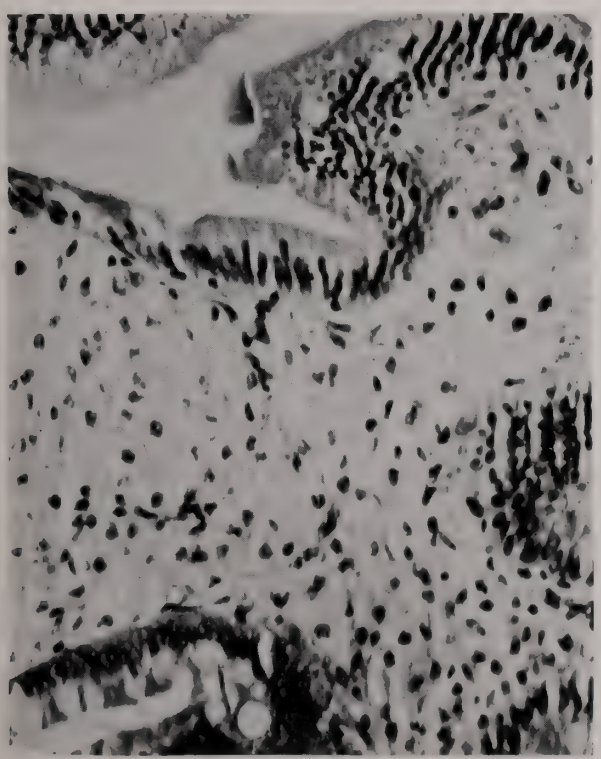


Fig. 4—Small bowel showing shortened and broadened villus and histiocytic infiltration (Hematoxylin and Eosin × 250).

and lymphadenopathy. Laboratory findings include steatorrhea and malabsorption, anemia, elevated sedimentation rate, and occult blood in the stool. Roentgenograms of the small intestine are characterized by coarsening of the mucosal folds with or without segmentation and flocculation.[3] Within recent years these features have been amplified, but little emphasis has been placed on the early diagnosis prior to the development of the full-blown syndrome. A patient is reported in whom the opportunities for early diagnosis were present but not utilized.

Intermittent Arthritis

This patient had intermittent arthritis over a 20-year period which probably represented the initial manifestation of this disease process. In Whipple's patient the migratory arthritis antedated other symptoms by more than five years. Kelly and Weisiger's review of 95 cases of Whipple's disease revealed arthropathy in at least two thirds of the cases.[4] When present, it usually precedes the other symptoms by several years. The joint symptoms characteristically consist of episodes of intermittent migratory arthralgia or arthritis, lasting several hours to several days, but then resolving

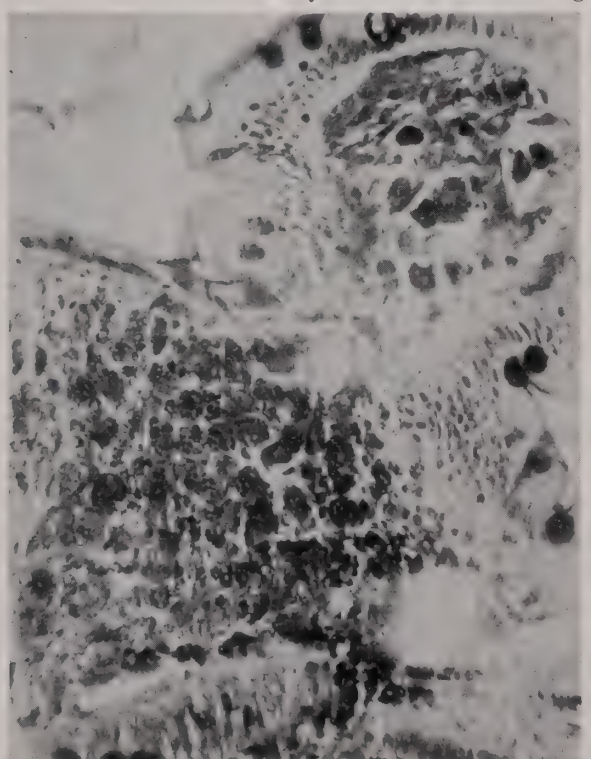


Fig. 5—Small bowel showing extensive PAS positive material (PAS stain × 250).

completely, leaving no residue. Long periods of remission from the arthritis during the early stage of the disease have been observed, and in some cases remission of the arthritis occurred with the onset of the abdominal symptoms.[5] Peripheral joints were most commonly involved and frequently this was bilateral. Spondylitis was found in almost 20% of the cases with Whipple's disease, all of whom had peripheral arthritis as well.

Periodic Acid Schiff's Positive Staining

Thus arthritis is often the earliest manifestation of Whipple's disease. The occurrence of nonspecific arthritis, especially associated with any of the other features of this syndrome should alert one to the diagnosis of Whipple's disease. Since Sieracki has reported periodic acid Schiff's (PAS)-positive inclusion bodies of the synovial lining cells,[6] biopsy of the joint with periodic acid Schiff's staining may prove to be a simple technique for establishing an early diagnosis.

Constipation

Profuse watery diarrhea is considered the cardinal manifestation of Whipple's disease. Although not infrequently the initial symptom, it is more commonly a late manifestation. Once diarrhea begins, the course is often one of progressive deterioration resulting in death. Constipation has not been emphasized; however, a review in 1950 reported over 25% of the patients to have constipation, either preceding the diarrhea or alternating with it.[7] There were also two patients with constipation who failed to develop diarrhea at any time during the course of the disease. Our patient initially had constipation, and only later developed diarrhea. Thus the absence of diarrhea does not exclude the diagnosis of Whipple's disease, and the presence of constipation may be the first or only gastrointestinal clue.

Skin Hyperpigmentation

Hyperpigmentation of the skin has not been adequately emphasized as a manifestation of Whipple's disease, although it was present in one half to two thirds of the reported cases.[8] Recent textbooks on dermatology do not mention Whipple's disease in the differential diagnosis of hyperpigmentation,[9,10] which is characterized by its marked variation in distribution and intensity. One study has commented that there are no reports of pigmentation without the presence of diarrhea.[11] Likewise in our patient, the pigmentation was not recognized until after the onset of the diarrhea. Although not usually reported in the prodromal period, subtle changes in pigmentation may well be present for some time before they are noted, a fact which may serve as an important clue in the early diagnosis of Whipple's disease.

Lymphadenopathy

Lymphadenopathy is found in 50% of the patients.[12] When combined with weight loss, fever, night sweats, and anemia there is a clinical resemblance to lymphoma, as is vividly illustrated in the present report, since the patient was initially treated for lymphoma. When lymphadenopathy is present, these nodes provide a readily available means of establishing the diagnosis. Histologic demonstration of periodic acid Schiff's-positive material is diagnostic and emphasizes the indication for this stain in cases of otherwise nondiagnostic lymph nodes (Figure 2).

Histopathology

While the presence of Whipple's disease may be suspected on clinical grounds, the diagnosis is established by histologic examination of lymph nodes, small intestinal mucosa, or possibly synovial membrane. With routine staining there are seldom characteristic morphological findings in these tissues (Figures 3 and 4). In 1949, Black-Schaffer demonstrated periodic acid Schiff's-positive macrophages within the small bowel mucosa.[13] These macrophages are considered to be the major diagnostic feature of the disease. They can be found in many tissues but are most prominent in the lamina propria of the small intestine (Figure 5). Other features in the small intestine are flattening or clubbing and fusion of the villi and the accumulation of fat-filled spaces in the mucosa;[14] but these features are of variable intensity and may be absent.

The recent demonstration of rod-shaped structures in and around the macrophages in jejunal biopsy specimens renewed interest in this disease.[15,16] Their presence has been confirmed in epoxy-embedded specimens under

light microscopy; they are not seen in routine paraffin sections. They are most abundant between macrophages, but individual bacilliform bodies have been seen within the cytoplasm of the macrophages.[14] With electron microscopy these rod-shaped structures have the typical fine appearance of bacteria.

Identity of Progressive Improvement

Following antibiotic treatment and during a period of remission, there is progressive improvement in the structure of the villi, disappearance of bacteria, and decrease in the number of periodic acid Schiff's-positive macrophages. Electron microscopy then reveals the absence of bacilliform structures.[17]

Thus, peroral small intestinal biopsy provides a specific method for establishing the diagnosis of Whipple's disease. It has proved to be a simple and safe procedure and should be considered in all cases of nonspecific arthropathy or enteropathy.

Bacteriology

Various bacteria have recently been isolated from patients with Whipple's disease and have been incriminated in its pathogenesis. Caroli et al. recovered a corynebacterium from an inguinal node,[18] Kok et al. isolated a corynebacterium and a hemophilus organism from the jejunum,[19] and Kjaerheim et al. demonstrated a hemophilus strain from intestinal mucosa.[20] Most recently, Charache et al. have grown atypical bacteria (bacteria with damaged or absent cell walls) from the blood and lymph nodes of a patient with Whipple's disease.[21] The presence or absence of this organism which proved to be a group D enterococcus correlated with the clinical status of the patient. These organisms could revert to typical bacterial form. It was suggested that "failure to identify this pathogen in the past may readily be explained by its presentation in atypical form."

Attempts to culture atypical forms in our case prior to treatment were unsuccessful; similar negative culture results are the rule in this disease. At this point no specific microorganisms can be incriminated as the etiologic agent in Whipple's disease. This is not to deny the role of these organisms, but only to emphasize the difficulties encountered in their isolation. Nevertheless, the possibility remains that the syndrome can be produced by several different organisms. Furthermore, certain host factors may play a significant role in the pathogenesis of the disease.

Summary

A patient with Whipple's disease provided the opportunity to emphasize the early manifestations of this syndrome. Nonspecific arthropathy may precede other manifestations by several years. Diarrhea is often a late symptom but may be absent entirely, while constipation may be the first or only gastrointestinal symptom. Furthermore, Whipple's disease should be considered in the differential diagnosis of hyperpigmentation of the skin. Lymph node biopsy or peroral small intestinal biopsy, when positive with periodic acid Schiff's stain, establishes the diagnosis in a clinically suspected case. Thus the means for early diagnosis are available for a disease which is potentially curable.

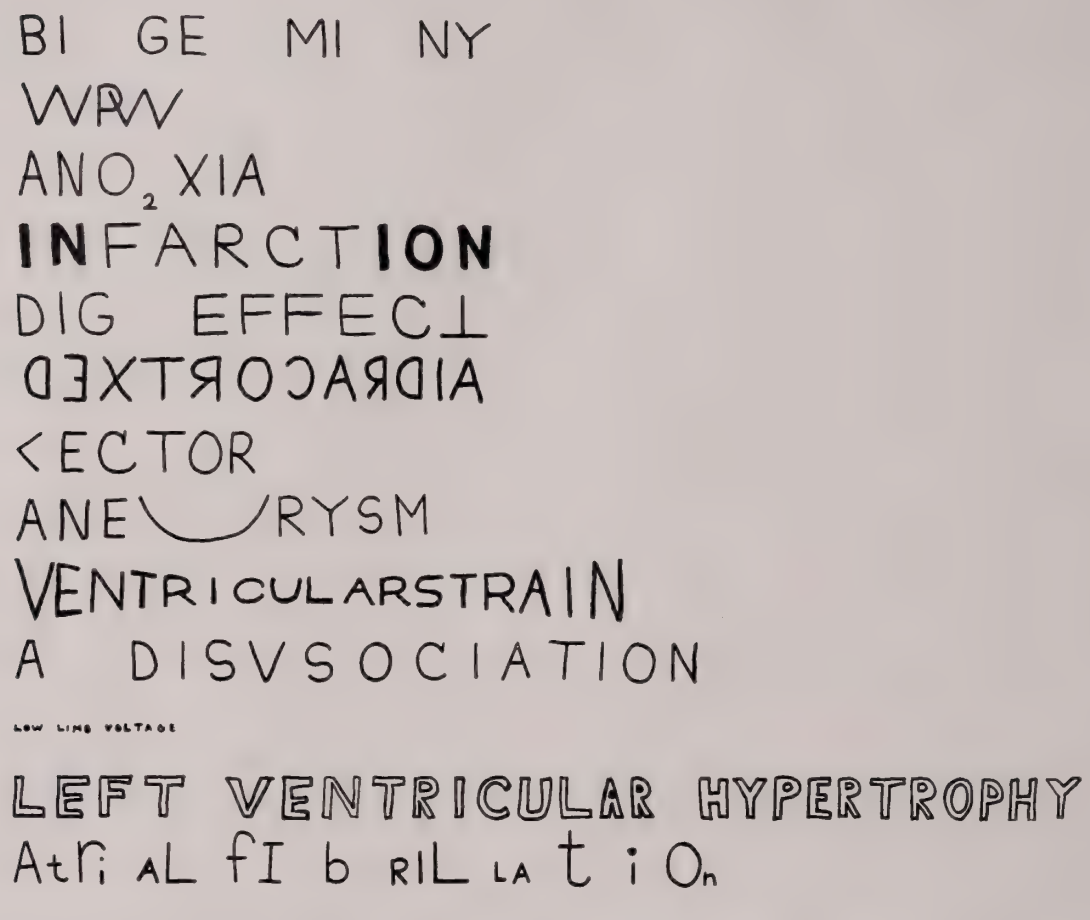
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It is only people of small moral stature who have to stand on their dignity.—Arnold Bennett

ELECTROCARDIOGRAPHICS



I am a second-year medical resident at the Minneapolis Veterans Administration Hospital. Last year, while reading electrocardiograms as a resident at Hennepin County General Hospital, I became fascinated with the way one could arrange electrocardiograph terms so that they demonstrated their meanings.

The above are some examples which I thought might be fun to publish.

Steven Strong, M.D.
Minneapolis, Minnesota

Strange Thing

A psychiatrist recently received a card from a patient vacationing at a resort: "Am having a wonderful time. Why?"—Kathy Gerson in Coronet.

Life is too short to be small.—Disraeli

Esophageal Resection*

Gastroesophageal Anastomosis

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RESECTION OF THE thoracic esophagus has become a frequent and standard surgical procedure. Following resection of the esophagus, the surgeon is presented with a difficult decision in determining what method of reconstruction would be best for a specific patient. Many methods have been described and are in varying degrees of use at this time. One of the choices for reconstruction is the utilization of the stomach transplanted into the chest.

This presentation concerns a recent review of records of patients who have undergone a specific operation involving the transplantation of the stomach into the chest. This procedure includes resection of the distal and mid-esophagus and anastomosis of the esophagus to the stomach, high within the thoracic cavity. Thus the stomach comes to reside within the thorax.

The patients include those seen in our surgical practice from January 1956 through January 1966, a 10-year period, 36 of whom have undergone this specific surgical procedure. Their records have been reviewed and constitute the substance of this report. All operations were either performed, or were directly supervised, by one of the members of this office.

History

The first successful surgical resection of a carcinoma of the mid-esophagus was accomplished by Dr. F. Torek[1] and was reported in 1913. This patient survived longer than five years and represents an apparent cure. No reconstruction was attempted, and the patient lived with a cervical esophagostomy and a gastrostomy. As recently as 1938, Dr. William Adams and Dr. Dallas Phemister found the reports of 17 such operations in the medical literature[2] and reported one additional case. In 1945, Dr. Richard Sweet of Boston presented a summary of nine cases of resection of the esophagus with reconstruction

*Presented at the Minneapolis Surgical Society Meeting, November 2, 1967, in Minneapolis.

utilizing the thoracic stomach.[3] Since that time, numerous additional reports have appeared in the literature.[4,5]

Technique

The operations performed in these 36 patients were basically similar, being varied only to meet certain individual requirements.

Abdominal Portion

A long midline abdominal incision is made, through which complete abdominal exploration can be accomplished and the presence and extent of abdominal metastases assessed. Next, the stomach is mobilized completely, including division of the left gastric and the left gastroepiploic arteries. The duodenum is also mobilized. The posterior surface of the stomach is completely freed, and the greater curvature is mobilized, preserving very carefully the right gastroepiploic artery. This vessel serves, subsequently, as the sole blood supply to the body of the stomach. During this procedure, the lymph-bearing tissues in the gastrohepatic ligament, and the periaortic area surrounding the celiac axis are mobilized with the stomach. A pyloroplasty, or a pyloromyotomy, is then performed. It is also helpful, during this phase of the operation, to mobilize and enlarge the esophageal hiatus.

Thoracic Portion

The next phase of the procedure is a thoracotomy, most commonly a right thoracotomy. Here the esophagus, with surrounding lymph-node tissue, is mobilized from the diaphragm to well above the gross extent of the lesion, which is then excised with an adequate margin of normal esophagus. An esophagogastric anastomosis is accomplished, high within the thoracic cavity. We feel that a plastic reconstructive procedure, at the gastroesophageal angle, is an extremely valuable adjunct. This plastic reconstruction simulates the normal gastroesophageal junction and minimizes postoperative reflux esophagitis and stricture. This procedure includes plication of the fundus of the stomach to the esophagus from the esophagogastric anastomosis superiorly 4 to 6 cm.

Indications

Malignancy of the esophagus or proximal stomach is the most common clinical indication for esophageal resection. Thirty patients with carcinoma (22 squamous-cell, eight adenocarcinoma) underwent this operation. Resection is sometimes indicated as a palliative procedure even though distant metastases can be detected preoperatively. Patients with stricture, benign tumors, perforation of the esophagus would be candidates for this procedure.

Diagnosis

Dysphasia was the most common complaint leading to the diagnosis of carcinoma of the esophagus. Twenty-nine of the 30 patients with carcinoma complained of varying degrees of difficulty swallowing. The lesion, in one case, was discovered on routine upper gastrointestinal x-rays for suspected duodenal ulcer. Esophagoscopy was performed on two patients. X-ray alone was sufficient to make the diagnosis in the other 28 patients. Dysphasia was also present in the six patients with benign disease; it was a chronic symptom in all, and had been present for over 30 years in one patient.

CASE REPORTS

Case 1

This 64-year-old lady had had dysphasia for two years. Approximately one year prior to our examination, she had had an esophagoscopy, which yielded a biopsy confirming squamous-cell carcinoma of the mid-esophagus. She was treated with cobalt irradiation, with an excellent symptomatic response for approximately eight months. Then symptoms of dysphasia reappeared, and several attempts at placement of a Mackler tube resulted in regurgitation of the tube and extreme discomfort. Resection of the esophageal lesion, with esophagogastrostomy high in the thorax, was carried out. At the time of the laparotomy, numerous liver nodules, as well as periaortic lymph-node involvement, were noted. This surgical procedure would thus be classified as a palliative resection. The lady was able to swallow on the third day post surgery and continued in a comfortable status for the next 12 months. She expired 13 months after the surgical procedure, having been ill for approximately three weeks, with gradual inanition and weakness.

Case 2

This 46-year-old gentleman represents the youngest patient in this series with carcinoma of the esophagus. He had been ill with upper abdominal discomfort for approximately four weeks, and gastrointestinal x-rays revealed a duodenal ulcer. A repeat examination, following intensive medical treatment, showed healing of the ulcer, but demonstrated a small ulcerated polypoid lesion in the distal esophagus (Figure 1). He

underwent esophageal resection and esophageal gastric anastomosis. The immediate postoperative response was satisfactory, but he expired 15 days after surgery with azotemia due to renal shut-down. Autopsy revealed the cause to be severe, chronic, preexisting renal disease, undoubtedly exacerbated by this extensive surgical procedure.

Case 3

This 59-year-old lady had suffered repeated gastrointestinal hemorrhages. She had also had symptoms of dysphasia and inability to swallow solid foods for 30 or more years. Four years prior to her esophageal resection, a Heller esophagomyotomy had been performed, which brought temporary relief from the symptoms; but severe and repeated gastrointestinal bleeding prompted re-evaluation (Figure 2). Resection of the massively dilated and hypertrophied esophagus and esophageal gastric reconstruction were carried out and she has remained symptom-free for two years.

Results

Six patients underwent the thoracic stomach operation for benign disease. Three had esophageal stricture, two achalasia,* and one, a leiomyoma of the distal esophagus. All six are well one to nine years after surgery. There were no postoperative deaths. One patient has required a single esophageal dilatation.

Thirty patients underwent the thoracic stomach operation for malignant disease (Table). Eight had an adenocarcinoma of the esophagus, or proximal stomach, while 22 were found to have squamous-cell carcinoma of the esophagus. There were four postoperative deaths immediately related to the surgical procedure. In addition, there were three late hospital deaths, including one pulmonary embolus on the 18th postoperative day, following an uneventful surgical recovery. Another patient expired following a cerebrovascular accident occurring on the 13th postoperative day. The third hospital mortality has previously been mentioned and was due to renal failure.

One patient died of causes unrelated to the surgical procedure (cerebrovascular accident) 11 months after surgery. Two weeks prior to his death there was no laboratory, clinical or x-ray evidence of metastatic disease.

Eleven patients died of metastatic tumor four to 26 months after the surgical procedure. There are three patients currently alive with evidence of metastatic tumor. *Seven patients are alive with no evidence of recurrent disease,* four of them five years or more follow-

*See Test Your Word Score Page 1367.

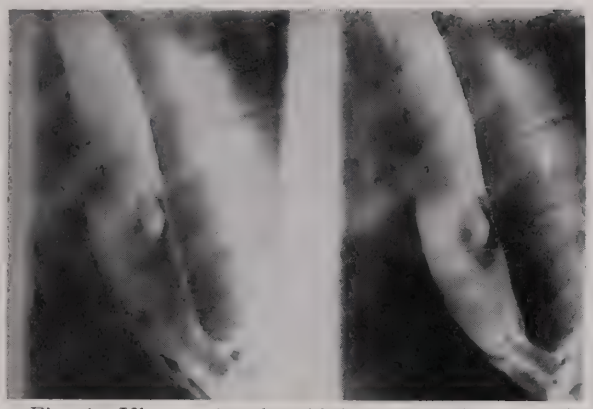


Fig. 1—Ulcerated polypoid lesion of distal esophagus.



Fig. 2—Dilated tortuous esophagus.

TABLE
Results—Esophageal Resection for Carcinoma

	No.	Percent
Postoperative death	4	13
Late hospital death	3	10
Dead—unrelated cause (11 months)	1	3
Dead—metastatic tumor	11	36
Alive—no evidence of residual tumor	7	23
Alive with known residual tumor	3	10
Lost to follow-up	1	3
	30	
Alive—no evidence of tumor five years or more post resection	4	13

ing surgery. One patient was lost to follow-up after three months.

Comments

Ischemic necrosis of the stomach was not encountered in any of the 36 patients. In the entire group there was one anastomotic leak, which resulted in empyema and postoperative death. Twenty-four patients survived one year or more, two of them requiring esophageal dilatation. The other 22 patients were relatively asymptomatic.

The majority of these patients underwent a period or readjustment of eating habits immediately after their surgical procedure. Diarrhea, felt to be due to the vagotomy, was common, but transient. Dyspnea with full meals was not encountered. Some patients required frequent small feedings. Several needed vitamin B-12 injections to maintain a satisfactory hematocrit.

Conclusions

The overall cure rate for carcinoma of the esophagus and proximal stomach is low. Despite this low cure rate, however, this operation offers many advantages. The surviving patients are comfortable and can breathe and eat normally. Long-term complications are rare. Esophageal resection, with gastroesophageal reconstruction, also offers an excellent method for management of the benign diseases of the esophagus which are not controlled by more simple means. We feel that this operation is tolerated well enough to be used for palliation on a selective basis, even in some very ill and wasted individuals. Surgical resection of esophageal carcinoma offers the only reasonable chance for a cure from this disease.

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Quick Energy

In great consumptions learn'd Physicions thinke,
'Tis good a Goat or Camels milke to drinke,
Cowes-milke and Sheepes doe well, but yet an Asses
Is best of all, and all the other passes.

—Regimen Sanitatis Salerni

Editor's Note: Here the school may well be taking a sly little dig at "learn'd" physicians for supposing that ass's milk surpasses that of cows, sheep, goats and camels in the treatment of wasting diseases. On the other hand they may have realized the value of quick energy from the increased carbohydrate content, and the similarity of ass's milk to mother's milk.*

*See Page 1446.

DERIVATIVELY SPEAKING

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Indication—Oral contraception.

Contraindications—Thrombophlebitis, thromboembolic disorders, cerebral apoplexy or a past history of these conditions, markedly impaired liver function, known or suspected carcinoma of the breast, known or suspected estrogen-dependent neoplasia, undiagnosed abnormal genital bleeding.

Warnings—Watch for the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, retinal thrombosis); if present or suspected discontinue the drug immediately.

British studies reported in April 1968[1,2] estimate there is a seven- to tenfold increase in mortality and morbidity due to thromboembolic diseases in women taking oral contraceptives. In these controlled retrospective studies, involving 36 reported deaths and 58 hospitalizations due to "idiopathic" thromboembolism, statistical evaluation indicated that the differences observed between users and non-users were highly significant. The conclusions reached in the studies are summarized in the table below:

Comparison of Mortality and Hospitalization Rates Due to Thromboembolic Disease in Users and Non-Users of Oral Contraceptives in Britain.

Category	Mortality Rates		Hospitalization Rates (Morbidity)
	Age 20-34	Age 35-44	Age 20-44
Users of Oral Contraceptives	1.5/100,000	3.9/100,000	47/100,000
Non-Users	0.2/100,000	0.5/100,000	5/100,000

No comparable studies are yet available in the United States. The British data, especially as they indicate the magnitude of the increased risk to the individual patient, cannot be applied directly to women in other countries in which the incidences of spontaneously occurring thromboembolic disease may differ.

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or sudden onset of proptosis, diplopia or migraine. Withdraw medication if papilledema or retinal vascular lesions are found.

Since the safety of Ovulen in pregnancy has not been demonstrated, it is recommended that pregnancy be ruled out for any patient who has missed two consecutive periods before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the first missed period.

A small fraction of the hormone agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

Precautions—Pretreatment physical examination should include special reference to the breasts and pelvic organs, and a Papanicolaou smear.

Endocrine and possibly liver function tests may be affected by Ovulen. Therefore, it is recommended that such tests if abnormal be repeated after the drug has been withdrawn for two months.

Pre-existing uterine fibromyomas may increase in size under the influence of progestogen-estrogen preparations.

Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

In breakthrough bleeding, and all irregular vaginal bleeding, consider nonfunctional causes. Adequate diagnostic measures are indicated in undiagnosed vaginal bleeding.

Carefully observe patients with a history of psychic depression and discontinue the drug if severe depression recurs.

Any possible influence of prolonged Ovulen therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study.

A decrease in glucose tolerance has occurred in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be observed carefully while receiving Ovulen.

Because of the effects of estrogens on epiphyseal closure Ovulen should be used judiciously in young patients in whom bone growth is not complete.

The age of the patient constitutes no absolute limiting factor, although Ovulen therapy may mask the onset of the climacteric.

The pathologist should be informed of Ovulen therapy when relevant specimens are submitted.

Adverse Reactions—A statistically significant association has been shown between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: cerebrovascular accidents, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, breast changes (tenderness, enlargement, secretion), change in weight, changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post partum, cholestatic jaundice, migraine, allergic rash, rise in blood pressure in susceptible individuals, mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme and nodosum, hemorrhagic eruption, itching.

The following laboratory results may be altered by oral contraceptives: hepatic function: increased sulfobromophthalein and other tests; coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X; thyroid function: increase in PBI and butanol extractable protein bound iodine, and decrease in T^3 values; metyrapone test; pregnanediol determination.

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Before prescribing see Detailed Product Information.

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Precautions: Until patient's response has been determined, he should be cautioned against engaging in operations requiring alertness. Administer with care to patients with cardiac or peripheral vascular diseases or hypertension.
Side Effects: Hypersensitivity reactions including skin rashes, urticaria, hypotension and thrombocytopenia, have been reported on rare occasions. Drowsiness, lassitude, nausea, giddiness, dryness of the mouth, mydriasis, increased irritability or excitement may be encountered.
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Editorials

Whipple's Disease

WHIPPLE'S DISEASE or intestinal lipodystrophy was considered a rare and incurable disease until recently. The etiology was unknown and the diagnosis could be confirmed only at laparotomy or autopsy. These concepts have been radically altered by observations made within the past few years as illustrated by the interesting case report of Bornstein, Theologides and Kennedy* in this issue of MINNESOTA MEDICINE.

As with other diseases of the small bowel, the study of Whipple's disease was greatly facilitated by the introduction and application of safe and effective intestinal biopsy technics. In 1958, Bolt et al.[1] reported the first case of Whipple's disease diagnosed in this manner, and by 1961 the tiny red-shaped structures in the lamina propria, described initially by Whipple in 1907, were found to have the ultra structural characteristics of bacilli.[2,3]

Simultaneously, clinical observations suggested that remissions could be induced by antibiotic therapy,[4] and subsequent study has shown that the bacilliform bodies of Whipple's disease disappear from the intestinal mucosa after appropriate therapy with antibiotics.[5] When serial biopsies were taken after an antibiotic-induced remission, it was found that the bacilli may reappear and, in the absence of further treatment, this was followed by clinical relapse. These observations are suggestive of an infectious etiology of Whipples disease.

Peroral intestinal biopsy is the diagnostic procedure of choice. Occasionally the diagnosis can be made by biopsy of a lymph node or the colon. Radiographic findings may be suggestive but are not diagnostic. In view of the potential curability of Whipple's disease, it should be considered in any patient with unexplained progressive wasting when coupled with malabsorption, lymphadenopathy or arthritis. Undoubtedly, the increasing clinical use of peroral biopsy of the small bowel will uncover cases of Whipple's disease before the clinical picture is entirely developed.

Current treatment consists of antibiotic therapy for a period of months. A regimen of 1,200,000 U. procaine penicillin G. and 1 gm. streptomycin daily for 10 to 14 days followed by tetracycline 1 gm. daily for 10 to 12 months has been effective.[6] Serial intestinal biopsies may prove useful in the evaluation of therapeutic success and in the prediction of relapse. Clinical remission is generally prompt and striking, as with the patient of Bornstein et al., although exacerbations have been reported after apparently inadequate antibiotic therapy.[5] In one case the organism appeared to show resistance to tetracycline but penicillin seemed effective. Corticosteroid therapy does not seem necessary although it has been useful in the treatment of persisting arthritis.

Arnold P. Kaplan, M.D.
Minneapolis, Minnesota

*See Page 1345.

References may be secured from the author.



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Inappropriate Secretion of Antidiuretic Hormone and Inappropriate Thirst

HYPONATREMIA, NATRIURESIS, and the inability to excrete a maximally dilute urine are hallmarks of the syndrome of inappropriate secretion of antidiuretic hormone. Their importance has been stressed since Schwartz and associates[1] first described the syndrome in 1957. The inability to excrete water normally is reflected in the formation of urine which is less than maximally dilute (and usually is hyperosmolar to serum) in the presence of hypo-osmolality of the serum and extracellular fluid. The hyponatremia cannot be corrected by dietary sodium supplements because natriuresis persists and sodium is lost, almost milligram for milligram, as it is administered. These abnormalities can be explained on the basis of an expanded extracellular fluid space and are accounted for by one or a combination of the following factors.

1. Increased glomerular filtration rate may occur with an expanded extracellular fluid space. This presents to the renal tubule extra sodium which is available for excretion. However, it has been amply demonstrated that natriuresis can still occur even if the renal artery is partially occluded, preventing an increased glomerular filtration rate.

2. Aldosterone excretion and secretion are reduced by an expanded extracellular fluid space, thereby encouraging the excretion of filtered sodium. But the administration of a full replacement dose (or more) of a potent mineralocorticoid does not prevent the sodium loss. In addition, when measured, aldosterone secretion and excretion have almost invariably been normal in this syndrome. Since neither of these first two factors can adequately explain the natriuresis, a "third factor" must be operative.

3. This third factor effect, mediated by a presumed humoral (or hormonal) agent of central nervous system origin, reduces the proportion of sodium reabsorbed in the proximal renal tubule in response to expansion of the extracellular fluid . This may occur even when the glomerular filtration rate is experimentally reduced or when mineralocorticoid is available in more than physiologic quantities.

4. Recent evidence[2] has suggested that the influence of antidiuretic hormone on membrane permeability may encourage sodium migration from an extracellular to an intracellular site, thus contributing to the hyponatremia.

The prime abnormality—namely, an expanded extracellular fluid space—is attributable to the excessive and inappropriate secretion of antidiuretic hormone. The renal loss of sodium cannot be explained by a direct action of antidiuretic hormone because, if the fluid intake is restricted so that water retention and weight gain do not occur, the serum remains normotonic with a normal sodium concentration. All the abnormalities of the syndrome can be easily reversed by the simple expedient of restricting fluid intake.

Very properly, Segar and Moore* have questioned the source of the "inappropriate thirst" that provides the water for overexpansion of the extracellular fluid space. Heretofore, this important aspect of the syndrome has not been emphasized; it raises significant questions regarding the physiologic control of so basic an urge as thirst. Hyperosmolality and hypovolemia result in thirst and are also associated with increased blood levels of antidiuretic hormone. Conversely, hypo-osmolality with an expanded extracellular fluid space is associated with suppression of antidiuretic hormone secretion and an increased excretion of free water. Thirst, however, is not necessarily diminished under these circumstances, and it is only the efficiency of the normal excretory mechanism for water that prevents the frequent occurrence of self-induced water intoxication. When the normal mechanism of water excretion is absent, as in the presence of excessive, nonsuppressible, inappropriate secretion of antidiuretic hormone, voluntary excessive fluid intake quickly leads to overexpansion of the extracellular fluid space with its resultant complications. Under these circumstances, there seems to be no control mecha-

*Segar, W. E., and Moore, W. W.: Hyponatremia: Increased Antidiuretic Hormone and "Inappropriate" Thirst in a Patient with Bronchogenic Carcinoma. Minnesota Med 51:625, 1968.

Before prescribing, see complete prescribing information in SK&F literature or *PDR*.

Contraindications: Glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal or bladder neck obstruction.

Precautions: Use cautiously in the presence of hypertension, hyperthyroidism, coronary artery disease; warn vehicle or machine operators of possible drowsiness.

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Note: The iodine in isopropamide iodide may alter PBI test results and will suppress I^{131} uptake; discontinue 'Ornade' one week before these tests.

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nism to prevent the unnecessary ingestion of water and to curtail the inappropriate thirst. Most intriguing of the authors' suggestions to explain this phenomenon is the conjecture that an increased antidiuretic hormone level in the blood is in itself a thirst-producing stimulus.

The authors are to be congratulated for emphasizing the importance of abnormal fluid ingestion in the development of the full syndrome of inappropriate secretion of antidiuretic hormone, a facet previously ignored. In addition, they have indicated an important hiatus in our knowledge of physiology of fluid volume control—namely, the mechanism of thirst regulation.

Horace K. Ivy, M.D.
Rochester, Minnesota

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2. Kaye, M.: An Investigation Into the Cause of Hyponatremia in the Syndrome of Inappropriate Secretion of Antidiuretic Hormone. Amer J Med 41:910, 1966.

Elusive Coarctation of the Aorta

THE REPORT of 18 cases of coarctation of the aorta in veterans by Sako and Beard[1] serves well to remind physicians of the possibility of overlooking this relatively easily diagnosed condition.

Since most of us have both undergone and given camp, preinduction, and discharge physical examinations in the typical crowded and noisy gymnasium, we are not too surprised at rather salient conditions being missed. On the other hand, in a most interesting clinicopathologic conference, another case reported in the October 1967 issue of *American Heart Journal* points out the difficulties encountered in the differential diagnosis under ideal circumstances of examination.

Interest in the mechanism of production of hypertension and the rather unique lack of resultant disease of the small vessels in coarctation has brought forth important articles in the recent literature. Several workers have shown normal renal blood flow and angiotensin levels, although Sealy[2] cited two cases in which angiotensin levels that were high before operation fell to normal after repair of the coarctation. Postoperative hypertension, especially diastolic, is common and may be associated with gastrointestinal symptoms secondary to ischemia and necrosis of the small bowel; both the hypertension and the gastrointestinal symptoms may be reversed with suitable antihypertensive therapy. The hypertension apparently results from increased response of vessels below the coarctation to the stress-induced elevation of norepinephrine.[3]

These recent studies suggest that the hypertension associated with coarctation results from both humoral and reflex factors, which adjust baroreceptors to hypertensive levels in order to maintain sufficient pressure above the obstruction and assure adequate flow beyond it.

Thomas T. Schattenberg, M.D.
Rochester, Minnesota

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Pathology

Ugliness is a point of view: an ulcer is wonderful to a pathologist.—Austin O'Malley

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Scalene Node Resection or Mediastinoscopy and Biopsy*

In 1959 MEDIASTINOSCOPY became a new diagnostic technique in unknown mediastinal or pulmonary disease. Extensive experience has proven the value and safety of this procedure. In many instances, mediastinoscopy should supplant scalene node resection as the diagnostic approach. There are ample statistics that indicate mediastinoscopy and biopsy obtain more positive tissue diagnoses for nonneoplastic and neoplastic disease than does scalene node examination.

However, *I most heartily disagree* with the statement that scalene node removal involves more morbidity and mortality than does mediastinoscopy. This latter statement results from several reports in the literature.[1,2] Review of these reports and others[3] indicates that the major causes of operative morbidity and mortality are technical errors during the procedure. Injury to major vessels, nerves, and lymphatics as well as air embolism have occurred. In most part technical failures resulted because the surgical procedure was delegated to an unskilled, untrained, and unsupervised house officer to do "a little biopsy." This important fact is noted in the reports. The same technical failures would erupt if mediastinoscopy were entrusted to the untrained, unsupervised individual.

There are specific indications for mediastinoscopy and/or scalene removal. Each remains a valuable diagnostic technique. Both procedures are complicated technical dissections that require the best of surgical skills. Both are equally safe.

Another misinterpreted statement concerns "resectability" of pulmonary neoplasms. The term "resectability" needs further clarification. "Resectability" for cure and a positive node biopsy for metastases by mediastinoscopy are *not* incompatible. It should *not* be assumed that a positive biopsy contraindicates (and "saves the patient" from) thoracotomy. Indeed, if this is the attitude, a sizable percentage of patients will be condemned in the effort to "save" them. I would refer interested readers to an excellent article by N. P. Bergh and T. Schersten.[4]

Patients with neoplasm fall into certain categories which can be determined by conventional x-rays and laminograms in most instances. Careful teamwork between the physician, surgeon, radiologist, oncologist, and pathologist will give the afflicted patient the best opportunity for a future.

Jerome Grismer, M.D.
Minneapolis, Minnesota

*Johnsen, A. F. et al.: Mediastinoscopic Diagnosis of Sarcoidosis. Minnesota Med 51:915, 1968.

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All modern men are descended from wormlike creatures, but it shows more on some people.—Will Cuppy

There is nobody so irritating as somebody with less intelligence and more sense than we have.—Don Herold

A little inflation is like a little pregnancy—it keeps on growing.—Leon Henderson

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Permanent Transvenous Cardiac Pacing*

THE DEVELOPMENT of permanent transvenous electrodes with implantable pulse-generator packs has provided a means of cardiac pacing that does not require a major operative procedure for the insertion of the electrodes. Under local anesthesia, the electrode is inserted into the external or internal jugular vein and advanced to the apex of the right ventricle. Fluoroscopic control is necessary for accurate positioning of the electrode tip. The pulse generator is placed in a pocket in the anterior chest wall. This procedure can be performed as the initial procedure in a patient requiring long-term cardiac pacing, without the preliminary insertion of a temporary pacer as is required when epicardial electrodes are used. The indications for cardiac pacing can now be extended to include those patients who require pacing but are considered to be poor risks for the major operative procedure required to implant epicardial electrodes.

Complications have been reported, as enumerated by Bilgutay and associates. Embolic episodes are uncommon and anticoagulant therapy is not necessary. Infection can usually be avoided by aseptic technique at the time of insertion, but this requires careful attention when the availability of fluoroscopy requires that the procedure be performed in areas other than the operating room. Erosion of an electrode through the skin usually occurs where the electrodes cross the clavicle and can be avoided if the electrode passes under the clavicle, especially in thin patients.

Accurate placement of the electrode tip allows effective and continuous pacing without perforation of the ventricle. In our experience, fracture of transvenous electrodes has occurred with less frequency than fracture of epicardial electrodes.

The complication of incarceration of an electrode in the trabeculae of the right ventricle is not common, because permanent electrodes seldom require removal. The successful removal of an incarcerated electrode by the method described by Bilgutay and associates obviates the need for a major operation which frequently would not be tolerated by patients who had been selected for transvenous pacing.

Robert B. Wallace, M.D.
Rochester, Minnesota

*Bilgutay, A. M., Jensen, N. K., Garamella, J. J., Schmidt, W. R., and Lynch, M. F.: Incarceration of Transvenous Pacemaker Electrode. Minnesota Med 51:489, 1968.

Test Your Word Score

Everted—*turned outward* (page 1327).

Xanthomata—*irregular yellow patches or nodules on the skin due to xanthoma or Rayer's disease* (page 1335).
(Rayer was a French physician who lived from 1793 to 1867.)

Achalasia—*failure to relax* (page 1353).

Hedonistic—*characterized by hedonism, the doctrine that pleasure is the chief good of life* (page 1371).

Psychoanalysis
Psychoanalysis is the disease it purports to cure.—Karl Kraus

---

Children have more need of models than of critics.—Joubert



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Indications: Mental depression and mild anxiety accompanying depression.

Contraindications: Glaucoma and predisposition to urinary retention. Not recommended in pregnancy.

Precautions and Side Effects: Drowsiness may occur within the first few days of therapy. Patients should be warned against driving a car or operating machinery or appliances requiring alert attention. When depression is accompanied by anxiety or agitation too severe to be controlled by ELAVIL HCl alone, a phenothiazine tranquilizer may be given concomitantly. Suicide is always a possibility in mental depression and may remain until significant remission occurs. Supervise patients closely in case they may require hospitalization or concomitant electroshock therapy. Untoward reactions have been reported after the combined use of antidepressant agents having varying modes of activity. Accordingly, consider possibility of potentiation in combined use of antidepressants. Monoamine oxidase inhibitor drugs may potentiate other drugs and such potentiation may even cause death; permit at least two weeks to elapse between administration of two agents; in such patients, initiate therapy with ELAVIL HCl cautiously with gradual increase in dosage required to obtain a satisfactory response. Caution patients about errors of judgment due to change in mood, and that the response to alcohol may be potentiated. May provoke mania or hypomania in manic-depressive patients.

Side effects include drowsiness; dizziness; nausea; excitement; hypotension; fine tremor; jitteriness; weakness; headache; heartburn; anorexia; increased perspiration; incoordination; allergic-type reactions manifested by skin rash, swelling of face and tongue, itching; numbness and tingling of limbs, including peripheral neuropathy; activation of schizophrenia which may require phenothiazine tranquilizer therapy; epileptiform seizures in chronic schizophrenics; temporary confusion, disturbed concentration or, rarely, transient visual hallucinations on high doses; evidence of anticholinergic activity, such as tachycardia, dryness of the mouth, blurring of vision, urinary retention, constipation; paralytic ileus; jaundice; agranulocytosis.

Careful observation of all patients is recommended. The antidepressant activity may be evident within 3 or 4 days or may take as long as 30 days to develop adequately, and lack of response sometimes occurs. Response to medication will vary according to severity as well as type of depression present. Elderly patients and adolescents can often be managed on lower dosage levels.

Supplied: Tablets ELAVIL HCl, containing 10 mg., 25 mg., and 50 mg. amitriptyline HCl, bottles of 100 and 1000; Injection ELAVIL HCl, in 10-cc. vials, containing per cc.: 10 mg. amitriptyline HCl, 44 mg. dextrose, 1.5 mg. methylparaben, and 0.2 mg. propylparaben.

For more detailed information, consult your Merck Sharp & Dohme representative or see the package circular.

MERCK SHARP & DOHME Division of Merck & Co. Inc. West Point Pa 19486

WHERE TODAY'S THEORY IS TOMORROW'S THERAPY

You May Be Right

There Was A Time

There was a time when childbirth and pregnancy were accompanied by grave dangers; when toxemia, infection and hemorrhage were commonplace and carried many young mothers to an untimely grave—and yet society forbade fetal destruction.

There was a time when syphilis was often transmitted from the infected mother to her unborn child, inflicting on this innocent victim lifelong physical disfigurement and heartbreaking handicaps—and yet society forbade termination of pregnancy, and instead gave encouragement to the medical profession making mandatory the early recognition and prompt treatment of all syphilitic mothers to prevent this tragedy.

There was a time when there were no reliable or acceptable methods of contraception, and without doubt the vast majority of pregnancies were unplanned and many quite inconvenient—and yet society protected the fetus against arbitrary destruction because it came upon the scene unsummoned.

There was a time when Rh isoimmunization wreaked untold havoc upon many babies, silently and without detectable warning. Now the process can be detected in the incipient stage, monitored in its progression, and thwarted by prompt intervention in nearly all cases. And within the past year, this tragic process has been found completely preventable by prompt immunization of the Rh negative mother with anti-Rh immune globulin. This substance is now universally available.

There was a time when the Rubella virus (German measles) infected a small percentage of pregnant mothers and occasionally damaged the fetus, sometimes severely, and there was no way of telling which mother was susceptible or of preventing the contagion. Now there is available a test showing which mother is susceptible to Rubella. Next year a vaccine to immunize against Rubella is expected. There need be no more Rubella babies.

There was a time when the additional burden of pregnancy was thought detrimental to the mother with heart disease, kidney disease, tuberculosis, or liver dysfunction. With the rapid technologic advance in controlling these diseases, pregnancy no longer constitutes an additional hazard.

Why then, in 1968, are we suddenly being told to ignore the foregoing medical progress and to exhibit less reverence for life than our preceding generations? Now that conception is purely optional, now that pregnancy and childbirth are unprecedentedly safe and comfortable, now that our society is more affluent than any in the history of man, why is it that volitional fetal destruction should be urged as an enlightened and progressive step? Have past generations stood firm against fetal destruction out of callous indifference to human suffering, or out of a deeply mature and fundamental reverence for life, including the right to live? As the medical indications for therapeutic abortion have been eliminated, only the psycho-social and economic

Smiles speak louder than words

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Milk-free, hypo-allergenic Soyalac has a pleasing taste that is eagerly accepted by most infants. It's similar to mother's milk in composition and assimilation, much like cow's milk in consistency and completely free of fibre. Extensive clinical data support Soyalac's value in promoting growth and development. Soyalac is also excellent for growing children and adults.



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indications remain; so why call this a medical problem. It is a social problem —an economic problem—but most of all, a problem of conscience. The society which encourages optional destruction of its offspring is not liberal, progressive or enlightened. It is instead hedonistic,* self-centered, and sick.

Proponents of popularizing legal abortion have found their most passionate argument to be the predicament of the innocent victim of rape or incest. Several facts must be set forth to put this problem in proper perspective. First, the transgression seldom occurs adjacent to ovulation, for the fertile time is but a small fraction of each month. Secondly, clinicians of wide experience have been repeatedly impressed with the rarity that conception follows an assault even at the theoretically fertile time. Finally, in the event that rape or incest is known to have occurred with certainty, two choices are available to the physician within the present scope of his license. He can prescribe an estrogenic substance for five days, rendering the uterine lining unsuitable for implantation, or he can remove the uterine lining by a simple dilatation and curettage. In either case, whether the ovum was fertilized is never known. Its ultimate "nesting site" having been denied pregnancy does not occur.

Where rape or incest is concealed, and only later alleged to have occurred, the need for deliberate investigation, careful documentation, and judicial decision is too obvious for comment. Rarely could these facts be assembled and properly weighed before the fetus was of such an age that destruction could no longer be called abortion. It would have to be termed destruction of a theoretically viable infant, and a stillbirth certificate would be required. In short, infanticide rather than abortion would be performed.

In summary, then, if society chooses to popularize legal abortion, let it not hide behind the pretext of rape, incest, or diseases which in the past proved uncontrollable. Let it forthrightly state that it intends to invite this procedure as a social convenience. But then let no one call this new, or progressive, or civilized, for it is none of these. It will be tacit public admission of our failure to take individual responsibility as members of society; and this is more than just regrettable; it is historically retrogressive, immature, and in the long run destructive of the integrity of our basic unit of society—the family.

J. L. Falls, M.D.
Red Wing, Minnesota

*See Test Your Word Score Page 1367.

The Worst Fooled Man

Is one who fools himself.
Is one who thinks profanity strengthens his arguments.
Is one who thinks his own case is peculiar.
Is one who thinks dirty money can buy a clean bill of health.
Is one who believes his own excuses.
Is one who thinks he can hoard his money and enjoy it.
Is one who believes his own flatterers.

—*Roy L. Smith*

Overweight

Let him who doesn't wish to die yet diet.

When it's more than a bad cold



your patient can feel better while he's getting better

Achrocidin®

Tetracycline HCl—Antihistamine—Analgesic Compound

Each tablet contains: ACHROMYCIN® Tetracycline HCl 125 mg.; Phenacetin 120 mg.; Caffeine 30 mg.; Salicylamide 150 mg.; Chlorothen citrate 25 mg.

In tetracycline-sensitive bacterial infection complicating respiratory allergy, ACHROCIDIN brings the treatment together in a single prescription—prompt relief of headache and congestion together with effective control of the organisms frequently responsible for complications leading to prolonged disability in the susceptible patient.

For children and elderly patients you may prefer caffeine-free ACHROCIDIN Syrup. Each 5 cc contains: ACHROMYCIN (Tetracycline) equivalent to Tetracycline HCl 125 mg.; Phenacetin 120 mg.; Salicylamide 150 mg.; Ascorbic Acid (C) 25 mg.; Pyrilamine Maleate 15 mg.

Contraindications: Hypersensitivity to any component.

Warning: In renal impairment, since liver toxicity is possible, lower doses are indicated; during prolonged therapy consider serum level determinations. Photodynamic reaction to sunlight may occur in hypersensitive persons. Photosensitive individuals should avoid exposure; discontinue treatment if skin discomfort occurs.

Precautions: Drowsiness, anorexia, slight gastric distress can occur. In excessive drowsiness, consider longer dosage intervals. Persons on full dosage should not operate vehicles. Nonsusceptible organisms may overgrow; treat superinfection appropriately. Treat beta-hemolytic streptococcal infections at least 10 days to help prevent rheumatic fever or acute glomerulonephritis. Tetracycline may form a stable calcium complex in bone-forming tissue and may cause dental staining during tooth development (last half of pregnancy, neonatal period, infancy, early childhood).

Adverse Reactions: *Gastrointestinal*—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. *Skin*—maculopapular and erythematous rashes; exfoliative dermatitis; photosensitivity; onycholysis, nail discoloration. *Kidney*—dose-related rise in BUN. *Hypersensitivity* reactions—urticaria, angioneurotic edema, anaphylaxis. *Intracranial*—bulging fontanels in young infants. *Teeth*—yellow-brown staining; enamel hypoplasia. *Blood*—anemia, thrombocytopenic purpura, neutropenia, eosinophilia. *Liver*—cholestasis at high dosage.

Upon adverse reaction, stop medication and treat appropriately.

Lederle

348-8

The Editor's Soliloquy

Elbow Steering

"How old are you?"
"About your age!"
"The 'ell you are!"
"The 'ell I aint!"
With that retort the datum seeking ended abruptly.

True, there are a few occasions when one must disclose his vital statistics: age, sex, medical history, driver's license credentials, life insurance data for the purpose of extrapolating probable longevity, eligibility to vote, collect social security, and hold political office,—well, that's about it! Otherwise, why date a man! If he is youthful and flexible in body and mind, he is young—chronology notwithstanding.

The compulsive reasons for wanting to know a man's age doubtless run the gamut from idle curiosity to idol worship. But whatever the reason, knowing the ages of your friends and associates has no more value than knowing the color of their knee joints. Who could care less!

I scarcely know the age of my own children. I know their birth *days;* but their birth *dates* don't concern me. Though a generation removed, they are my contemporaries, with whom I visit, discuss, socialize, philosophize, ski, dance the Watusi, hunt, fish, laugh and cry. Likewise the ages of my confreres are equally irrelevant within my frame of reference.

I can walk unassisted—without the guidance of someone beside me. Arm-in-arm camaraderie—yes; but elbow steering—no tank you!

Carl O. Rice, M.D.

Old Doc Hess: Hate makes for poor company at breakfast.—COR

The obvious is that which is never seen until someone expresses it simply.—Kahlil Gibran

---

There is nothing more beautiful in this world than a healthy wise old man.—Lin Yutang

---

The Progress Notes of Hippocrates

Criton,* in Thasus,† while still on foot, and going about, was seized with a violent pain in the great toe; he took to bed the same day, had rigors and nausea, recovered his heat slightly, at night was delirious. On the second, swelling of the whole foot, and about the ankle erythema, with distention, and small bullae (phlyctaenae); acute fever; he became furiously deranged; alvine‡ discharges bilious, unmixed, and rather frequent. He died on the second day from the commencement.—Hippocrates

Editor's Diagnosis: Gout.

---

*A citizen of ancient Greece.
†A Greek island in the Aegean Sea.
‡Intestinal.

Letter to the Editor

Dr. Charles Lick was up to see me regarding what he termed a misinterpretation of his case report as published in MINNESOTA MEDICINE in June 1968*— I don't know if you want to contact him on this or not but it would be a very gracious thing to do.

John H. Moe, M.D.

*Page 809.

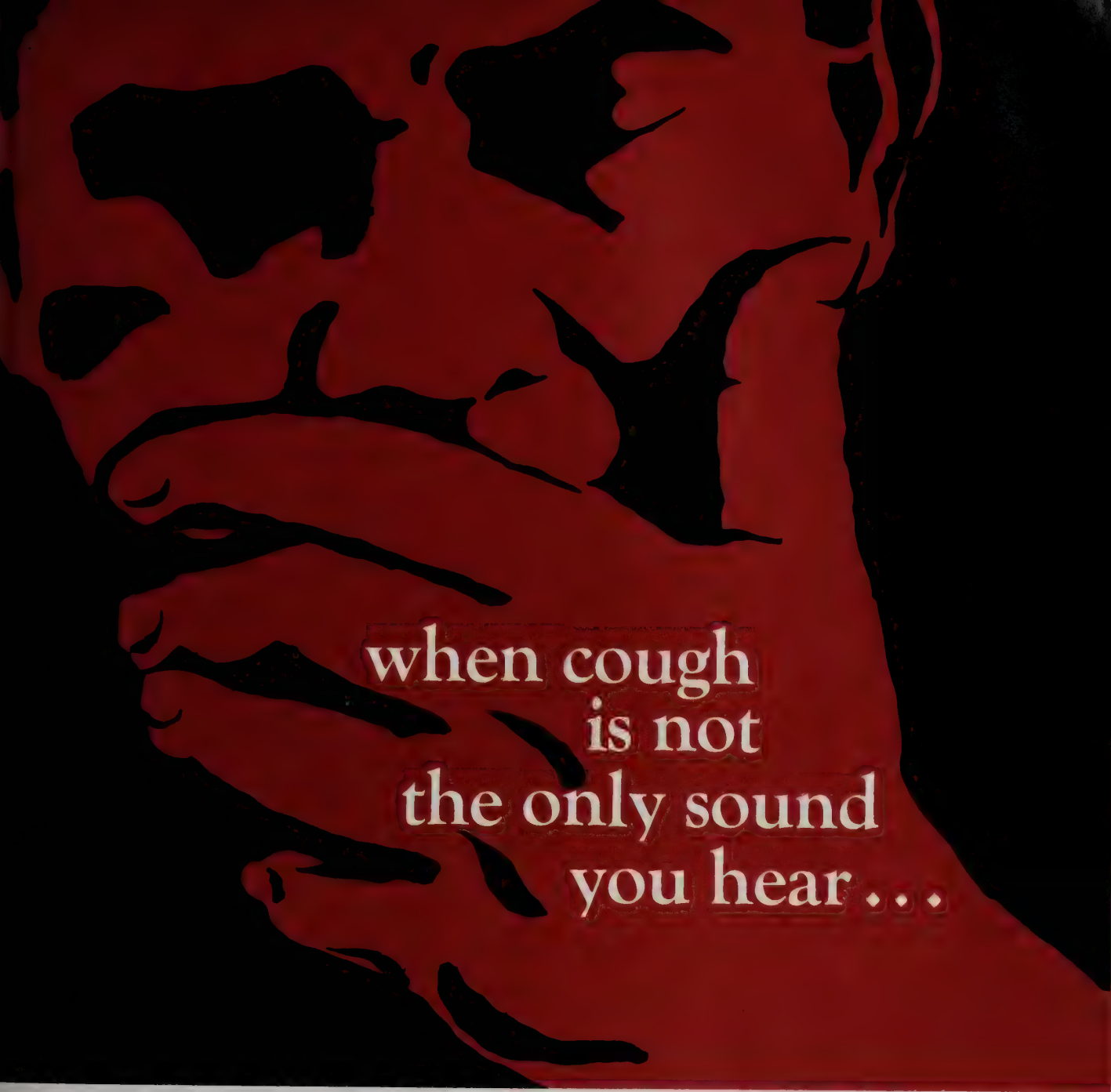
Dear Dr. Lick:

I have received the enclosed correspondence from Dr. John H. Moe and I sincerely regret that MINNESOTA MEDICINE misinterpreted your case report which should have stated in part, "Discussed the matter with Dr. Bell, who suggested that amputation should be considered. Called two experts in who advised amputation at the shoulder. Husband refused. I discussed the matter with her husband of a lesser procedure—that of removing the tumor with a liberal area of the radius above and below the tumor, to be followed by a radial transplant, a length enough to be a trifle longer than the gap. This was agreed upon by the husband—"

I am indeed sorry and hope that it has not caused too much inconvenience.

Carl O. Rice, M.D.
Editor-in-Chief





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. . . **because** OMNI-TUSS is indicated for cough associated with upper respiratory tract infections, bronchitis, bronchiectasis, bronchial asthma, emphysema, sinusitis and rhinitis, hay fever, or other allergic conditions. Any of these conditions may exhibit the general symptom syndrome—coughing, wheezing, bronchospasm, and tenacious mucus—which may benefit from the antitussive, bronchodilative, antihistaminic, and expectorant action of Omni-Tuss.

The therapeutic usefulness of Omni-Tuss is enhanced by a unique resin complex formulation providing the clinically desirable advantages of: (1) uniform drug availability throughout an extended period, (2) 8 to 12 hours of symptomatic control, (3) minimal dosage requirement, (4) minimal side effects.

Economical, efficient **b.i.d.** dosage—extremely well-tolerated by children, 6-12, and adults.

'Omni Tuss' Suspension: Each teaspoonful (5 cc.) contains 10 mg. codeine (Warning: May be habit-forming), 5 mg. phenyltoloxamine, 3 mg. chlorpheniramine, 25 mg. ephedrine, all as cation exchange resin complexes of sulfonated polystyrene, and 20 mg. guaiacol carbonate.

Available on prescription only. Class X exempt narcotic. Permissible on oral prescription.

Dosage: *Adults:* 1 teaspoonful (5 cc.) q12h.
Children (6-12 *years*): ½ teaspoonful q12h.

Side Effects: Minimal, but when encountered may include jitteriness, nausea, drying of mouth, insomnia, constipation, which disappear upon adjustment of the dose or discontinuance of treatment.

Precautions and Contraindications: For complete detailed information, refer to package insert or official brochure.

Strasenburgh

Strasenburgh Laboratories Division
Wallace & Tiernan Inc., Rochester, N.Y.

In the complex picture of moderate to severe anxiety...



there is a new reason for prescribing Mellaril (Thioridazine HCl)

effectiveness in mixed anxiety-depression

Long recognized for its usefulness in the treatment of moderate to severe anxiety, Mellaril is now also known to be effective against mixed anxiety-depression.

Often the symptoms of anxiety states are difficult to sort out—even with the most careful probing. The patient may manifest symptoms of agitation, restlessness, insomnia, somatic complaints. But what of the depression that may be mixed in the total picture? It is reassuring to know that Mellaril may be prescribed—with strong possibilities of success—when there is anxiety alone or a mixture of anxiety and depression.

Before prescribing or administering, see Sandoz literature for full product information, including adverse reactions reported with phenothiazines. The following is a brief precautionary statement.

Contraindications: Severe central nervous system depression, comatose states from any cause, hypertensive or hypotensive heart disease of extreme degree.

Warnings: Administer cautiously to patients who have previously exhibited a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) to phenothiazines. Phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides. During pregnancy, administer only when necessary.

Precautions: There have been infrequent reports of leukopenia and/or agranulocytosis and convulsive seizures. In epileptic patients, anticonvulsant medication should also be maintained. Pigmentary retinopathy may be avoided by remaining within the recommended limits of dosage. Administer cautiously to patients participating in activities requiring complete mental alertness (e.g., driving). Orthostatic hypotension is more common in females than in males. Do not use epinephrine in treating drug-induced hypotension. Daily doses in excess of 300 mg. should be used only in severe neuropsychiatric conditions.

Adverse Reactions: *Central Nervous System*—Drowsiness, especially with large doses, early in treatment; infrequently, pseudoparkinsonism and other extrapyramidal symptoms; nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache. *Autonomic Nervous System*—Dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, nasal stuffiness, and pallor. *Endocrine System*—Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema. *Skin*—Dermatitis and skin eruptions of the urticarial type, photosensitivity. *Cardiovascular System*—Changes in the terminal portion of the electrocardiogram have been observed in some patients receiving the phenothiazine tranquilizers, including Mellaril (thioridazine hydrochloride). While there is no evidence at present that these changes are in any way precursors of any significant disturbance of cardiac rhythm, several sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients previously showing electrocardiographic changes. The use of periodic electrocardiograms has been proposed but would appear to be of questionable value as a predictive device. *Other*—A single case described as parotid swelling.

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(Thioridazine HCl)
25 mg. t.i.d.

for moderate to severe anxiety and mixed anxiety-depression

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"The inconvenience of a cold"

For a cold, NTZ® Nasal Spray provides rapid relief of nasal symptoms. Relief starts with the first spray which opens the inferior part of the common meatus. A second spray, a few minutes later, will shrink the turbinates to help provide sinus drainage and ventilation. Dosage may be repeated every three or four hours as needed, for temporary relief of symptoms. NTZ is well tolerated but overdosage should be avoided.

As a sinusitis deterrent, NTZ Nasal Spray can be used to keep the nasal passages open during a cold to help prevent development of acute sinusitis—or to help prevent the acute condition from becoming chronic.

Supplied: NTZ Nasal Spray, plastic squeeze bottles of 20 ml.; NTZ Nasal Solution, bottles of 30 ml. (1 fl. oz.) with dropper.

NTZ is more than a simple vasoconstrictor. It contains

Neo-Synephrine® (brand of phenylephrine) HCl 0.5 per cent, the major component, virtually synonymous with fast, efficient but gentle nasal vasoconstriction.

Thenfadil® (brand of thenyldiamine) HCl 0.1 per cent, topical antihistamine for reduction of rhinorrhea, sneezing or itching. It combats the allergic reactions that may occur in colds or sinusitis.

Zephiran® (brand of benzalkonium, as chloride, refined) 1:5000, antiseptic preservative and wetting agent to promote penetration and spread of the formula.



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Curbstone Consultation

INDIRECT MEASURMENT OF BLOOD PRESSURE

QUESTION: Are there any methods presently available for the indirect measurement of blood pressure?

ANSWER: Yes. A method has been developed by Dr. Ray Ware and associates of Southwest Research Institute in San Antonio for measurement of blood pressure indirectly utilizing the Doppler principle* to detect movement of the artery occurring as a result of the pressure pulse caused by the expulsion of blood from the heart. The ultrasonic† detector, attached to the inner side of the blood pressure cuff, directs a narrow, ultrasonic beam through the patient's arm (leg) to the artery. If the artery is not moving, as would be the case with full occlusion, the frequency of the reflected beam would remain constant. When the beam is reflected from a moving artery its frequency changes and is detected and converted to a sound or to a deflection on a recorder.

As the cuff pressure is slowly released, a pressure is reached (systolic pressure) that is great enough to force open the occluded artery. This causes a single sound or deflection on the recorder and is analogous to the onset of the Korotkoff sounds. As the cuff pressure is further reduced, sounds or deflections of longer duration occur, caused by a larger percentage of the pressure pulse forcing its way through the occluded artery. When the cuff pressure is reduced to the point where the sounds or the deflections become continuous, diastolic pressure has been reached. This is analogous to the disappearance of the Korotkoff sounds. Although still in the experimental stage, the measurements made with it correlate closely with intra-arterial pressure measurements, and it thus holds great promise for future clinical use.

Edson H. Rafferty, B.S. (Mech. Eng.)
Biomedical Engineer
Houston, Texas

*Doppler principle: The frequency of a sound emitted from a source varies with the motion of the source.
†Ultrasonic: High frequency sound waves above the range of human hearing.

To cure nine out of ten neuroses, take hard work in heavy doses.—Cincinnati Inquirer

---

Refuse to be ill. Never tell people you are ill; never own it to yourself. Illness is one of those things which a man should resist on principle at the onset.—Bulwer-Lytton

Q. How much does the **anticostive*** **hematinic** cost?

A. No more than costive hematinics cost!

The anticostive hematinic is

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A tablet-a-day provides:

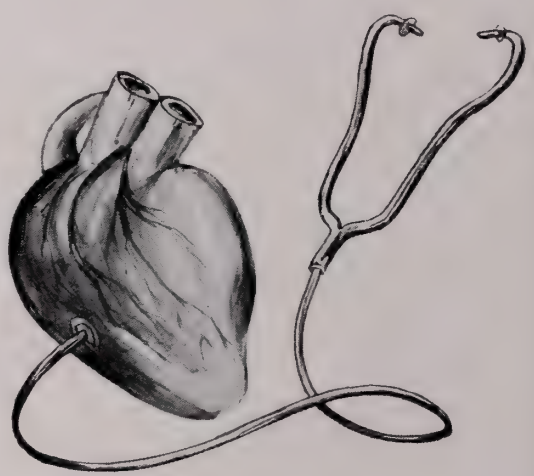
● Elemental Iron (as Ferrous Fumarate)	100 mg
● Dioctyl Sodium Sulfosuccinate (to counteract constipating effect of iron)	100 mg
Vitamin B_1	7.5 mg
Vitamin B_2	7.5 mg
Vitamin B_6	7.5 mg
Vitamin B_{12}	50 mcgm
Vitamin C	200 mg
Niacinamide	30 mg
Folic Acid	0.05 mg
Pantothenic Acid	15 mg

Bottles of 60

* anticostive, *adj.* (*anti* opposed to + *costive* causing constipation.) Against constipation. Now isn't that a good idea in an iron-containing hematinic?

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The Viewing Box

Asymptomatic 61-Year-Old Male

THIS RADIOGRAPH (Figure 1) is a scout film prior to intravenous pyelography on an asymptomatic 61-year-old male.

What is your diagnosis? (See next page.)



Figure



Diagnostic Products Sales, The Dow Chemical Company, Midland, Michigan 48640.

You won't have to wait for these results to come back from the lab. Because now you can do blood chemistry tests in your own office. With Diagnostest* reagents and instruments. You get accurate, precise results in minutes. And we teach your nurse or medical assistant to do the tests. The system can be used to measure hemoglobin, glucose, cholesterol, urea nitrogen, total bilirubin and uric acid. Write today for full details.

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DOW

Diagnosis: Diabetes mellitus.

Note the marked calcification of the vas deferens on each side (arrows). This calcification is almost pathognomonic of diabetes mellitus. Tuberculous infection of the genitourinary tract has been described as a cause of radiographic calcification of the vas but this is much less common as an etiologic factor than is diabetes.

Degenerative osteophyte formation in the lumbar spine and calcification of some of the pelvic blood vessels is also seen. Vascular calcification is a common finding in diabetes of long standing but is not specific and not too helpful in making the diagnosis unless the patient is under the age of 40 years.

Calcification of the vas deferens was first reported by Bianchini in 1930. In 1951 Wilson and Marks reported 60 cases of calcified vas deferens; of these, 56 were in diabetics of long standing. More recently, Kellett reported 215 cases, 98% of which were in diabetics.

The physiologic mechanism of this calcification in the muscular wall of the vas in diabetics is unknown but is felt to be related to the degenerative process associated with diabetes. Most, but not all of these patients are said to be impotent.

Patrick Malone, M.D.*
Minneapolis, Minnesota

*Departments of Radiology, Veterans Administration Hospital and Hennepin County General Hospital.

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2. Kellett, Mirle A., Radiologic Features of Diabetes Mellitus. Radiologic Clinics of North America. 5:239, August 1967.

C. F. Yeager, M.D.

Dr. C. F. Yeager was born in Reading, Pennsylvania, in 1903. His medical degree was obtained at Hahnemann Medical College, Philadelphia, in 1933. A Diplomate of the American Board of Preventive Medicine and Medical Director of the Remington Arms Co., Inc., for thirty-four years, Dr. Yeager specializes in occupational medicine and hygiene.

He is a member of the American Physicians Art Association and has received several awards for colored prints submitted at the annual conventions of the American Medical Association.

The cover photo was taken with a Leica M3, using Kodachrome X film.

I sometimes wish that people would put a little more emphasis upon the observance of the law than they do upon its enforcement. It is a maxim of our institutions that the Government does not make the people, but the people make the Government.—Calvin Coolidge.



After the picnic even Gramps Was a victim of intestinal cramps

Parepectolin for quick relief of acute diarrhea
...soothes colicky pain with paregoric*
...consolidates fluid stools with pectin
...adsorbs irritants with kaolin,
and protects intestinal mucosa

In elderly patients it is particularly important to stop the diarrhea fast. Parepectolin helps you control diarrhea promptly and gain the patient's confidence until etiology has been determined.

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Each fluid ounce of creamy white suspension contains:
*Paregoric (equivalent) ..... (1.0 dram) 3.7 ml.
Contains opium (¼ grain) 15 mg. per fluid ounce.
warning: may be habit forming
Pectin ..... (2½ grains) 162 mg.
Kaolin (specially purified) .... (85 grains) 5.5 Gm.
(alcohol 0.69%)
Usual Adult Dose: One or two tablespoonfuls three times daily.

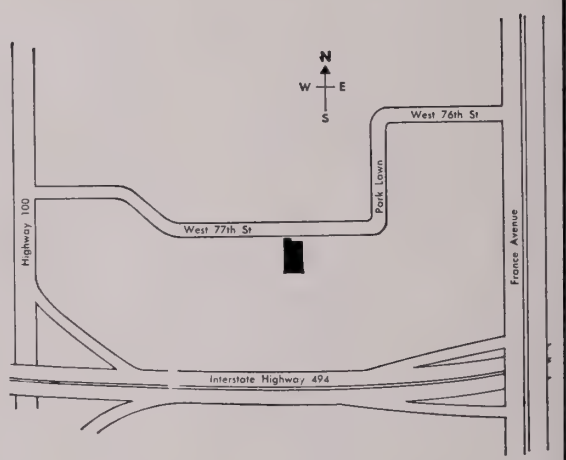
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Fracture Conference

Severe Fractures of the Ankle*

Dr. Lee C. Detenbeck:†

The subject of this fracture conference is methods of treatment for various severe fractures involving the ankle joint. Two cases will be presented. Case 1 is that of a 68-year-old farmer who sustained a fracture of his right ankle in December 1965, when a tractor rolled over on his leg (Figure 1). Essentially this is a trimalleolar fracture of the right ankle. The circulation is intact; both pedal pulses are present. The ankle was treated by injection of a local anesthetic agent into the fracture site and reduction of the fracture in the emergency room by realigning the foot with the tibia and gently molding the medial and lateral malleoli into proper position.

Dr. William H. Bickel:‡

The point to be made is that he had this trimalleolar fracture because he had intact ligaments. If the ligaments are ruptured, no fractures result in most cases. So it is always desirable to do just as was done in this instance: try to use the intact ligaments to pull the disrupted bony fragments back into line. Often with proper manipulation of the ankle they will fall in line just as they have here. This is an excellent reduction. I would accept it as it is.

While we are talking about trimalleolar fractures we should mention that the term "trimalleolar" is one Dr. M. S. Henderson coined in an article he published in the *Wisconsin Journal of Medicine* about 1938. He recognized the posterior flare of the distal tibia as the "third malleolus." The external and internal malleoli are obvious. He also discussed the fact that in trimalleolar fracture the ligaments are intact and the disrupted bone surfaces will follow the ligaments if one manipulates the foot into proper alignment with the leg. Sometimes this does not happen; then one can resort to an open reduction.

---

*Fracture conference held March 18, 1968.

†Mayo Graduate School of Medicine (University of Minnesota), Resident in Orthopedic Surgery.

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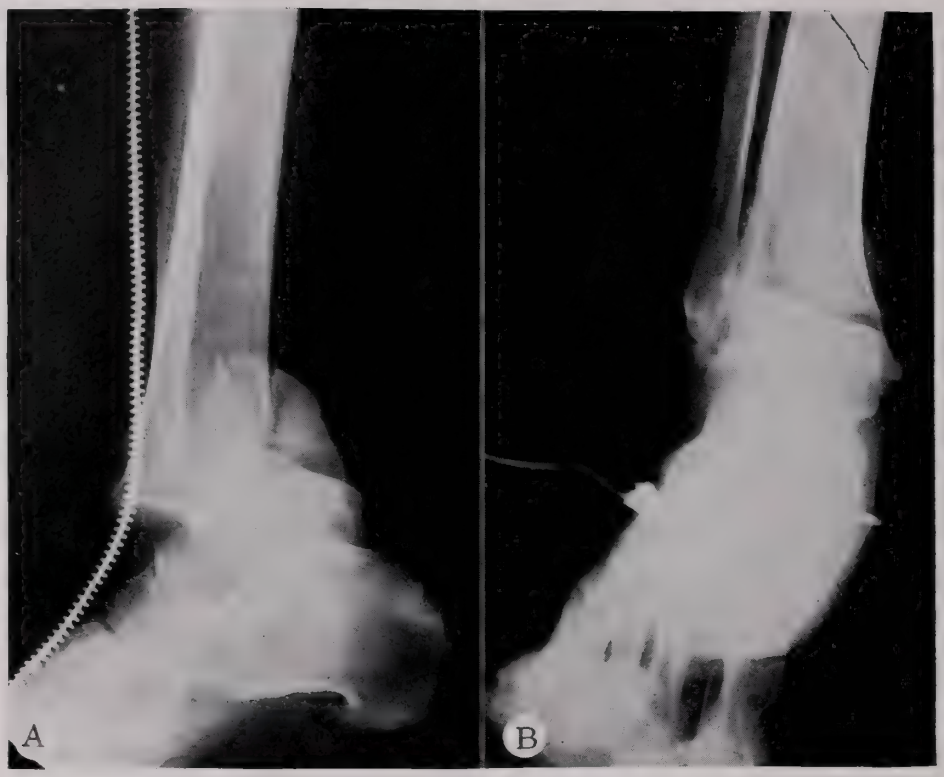


Fig. 1 (Case 1)—A and B, Acute fracture-dislocation of right ankle.

See page 1470 for Figure 1C and D, After closed reduction. Reduction is accepted.

(Authors sent figure in too late for inclusion in article, but asked that it be published elsewhere in journal.)

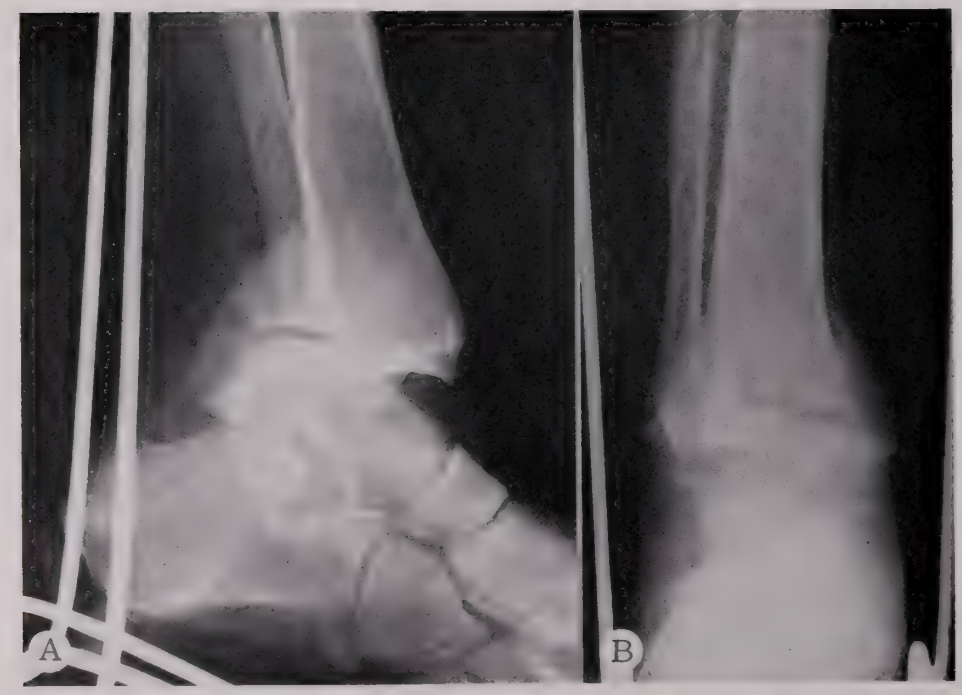


Fig. 2 (Case 1)—A and B, Three days after closed reduction. Note that position has been lost. Open reduction was necessary.

Dr. Detenbeck:

Roentgenograms made three days later revealed loss of the reduction and a return to the dislocated state. Open reduction seemed to be indicated, and four days after the fracture, open reduction and internal fixation of the internal malleolus were carried out, with the application of a long leg cast (Figure 2).

Dr. Mark B. Coventry:*

I wish we had a roentgenogram of the other ankle. This is an odd-looking ankle; there is something different about it. The talus is very broad. Is there any comment on it by the radiologist?

Dr. Ray E. Santos:†

I reduced this fracture in the emergency room and thought that things had turned out quite well. However, Dr. Bickel told me the next morning, "It will never hold. It will never stay there. I'll show you in a few days." Three days later, on re-x-ray examination, my fine reduction had "evaporated."

Dr. Coventry:

How did you hold the fracture from the time of reduction in the operating room until three days later?

Dr. Santos:

We held it in a modified Robert Jones dressing. That is where we made our mistake—the use of a dressing with so much padding that maintenance of the fragments was not possible.

Dr. Coventry:

I would not exactly blame the fracture. If you had put it in a good cast and bivalved it right away, maybe it would have remained reduced.

Dr. Santos:

We thought that there was so much swelling and ecchymosis that use of a cast at that time would not be safe. I know that the Robert Jones dressing is certainly not adequate fixation. We had a lot of difficulty with the posterior malleolus in trying to get it restored anatomically.

Dr. Bickel:

Holding it down, you mean?

Dr. Santos:

Yes.

Dr. Bickel:

On occasion, dorsiflexion of the great toe, putting tension on the long flexor, will help reduce and hold the posterior malleolus. What about the other ankle?

Dr. Santos:

We did not x-ray it.

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Dr. Coventry:

Were you ever concerned that this looked different from the average fracture?

Dr. Santos:

Yes. We opened it up and Dr. Bickel had his difficulties. There was more comminution than was obvious on x-ray examination.

Dr. Bickel:

Four days after reduction the fracture had slipped and open reduction and internal fixation were necessary.

Dr. Detenbeck:

A subsequent roentgenogram taken three months after the fracture (Figure 3) revealed a good result. The cast was then removed and the patient started weight-bearing.

Dr. Bickel:

I believe that one has to be cautious in interpreting this as a good result at this early date, as one can see from the checkup roentgenograms that there appears to be a little valgus of the astragalus in the anteroposterior and the lateral views, and the posterior malleolus does not appear to be perfectly reduced, though it seems to be united. I believe that time will have to tell how well this ankle is going to hold up. Not necessarily referring to this metal, but in regard to all metal around a joint, I would be interested in opinions on what to do with it. Should it be removed? What do you think, Dr. Peterson? Would you leave this metal in place?

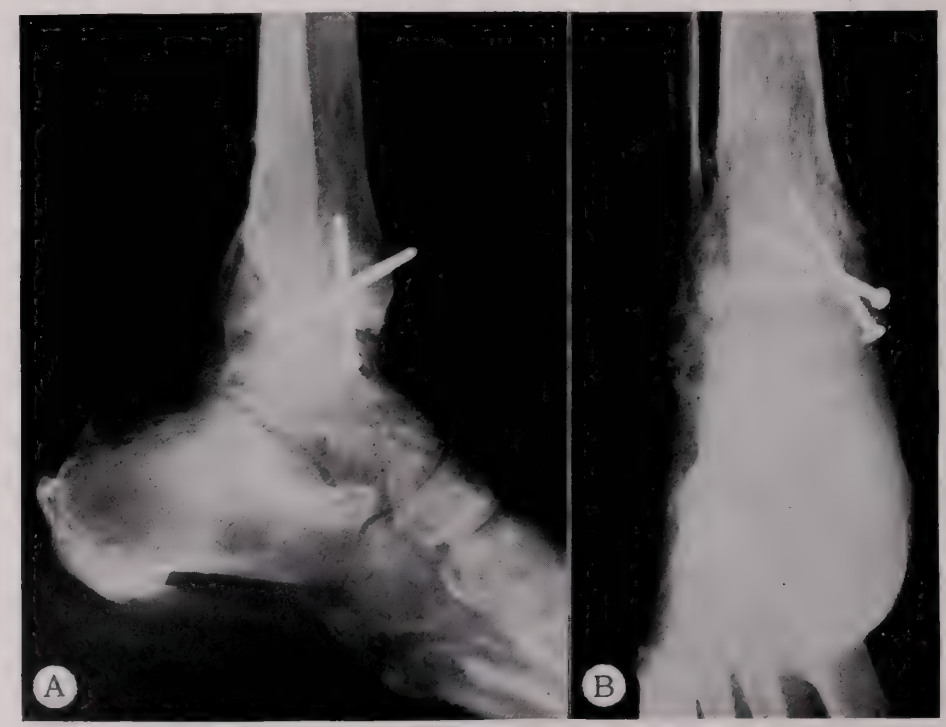


Fig 3 (Case 1)—A and B, Appearance three and a half months after open reduction and internal fixation.

Dr. Hamlet A. Peterson:*

Unless the patient is quite elderly, I think it should come out. It has served its usefulness for one purpose. Possibly it could act as a focus of infection if the patient had septicemia or something of this nature. Also, it might be a factor in any future degenerative or traumatic arthritis. In general, I think that the metal should be removed in the fairly young patient.

Dr. Bickel:

Regardless of whether the patient has symptoms?

Dr. H. Peterson:

Yes.

Dr. Bickel:

How do you feel, Dr. Janes?

Dr. Joseph M. Janes:†

I have never taken screws out unless the head of the screw is subcutaneous and is bothering the patient.

Dr. Anthony J. Bianco, Jr.:‡

I feel the same as Dr. Janes. Particularly with screws, I do not see any reason for removing them unless they are causing trouble.

Dr. Bickel:

You are speaking specifically about screws in the medial malleolus now?

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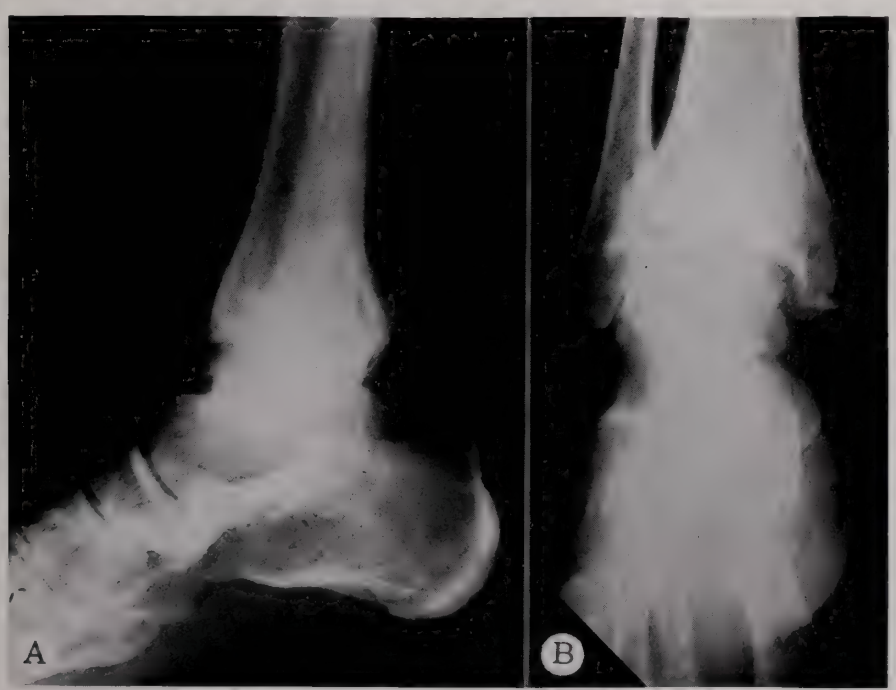


Fig. 4 (Case 2)—A and B, Right ankle 22 months after fracture and open reduction of medial malleolus, showing traumatic arthritis.

Dr. Bianco:

Yes. The ones I have removed have been removed because the screw head was under the skin and was bothering the patient.

Dr. Paul R. Lipscomb:*

It looks as if the one screw that is lying diagonally might give some trouble. I don't know.

Dr. Bickel:

Well, we have two opinions: leave the screws in place, and take them out. I let sleeping dogs lie.

Dr. Coventry:

I feel that today, with the use of vitallium, there is no need to take the screws out unless there is something factitial that could be explained by their presence. Incidentally, taking out some of these screws is not easy. The one placed posteriorly at the time of open reduction in this case might be difficult to remove and some damage might result. I had to remove some like this in the process of doing an ankle arthrodesis not long ago. To get the screw out, I had to retract the posterior tibial nerve. When the screw was put in, the nerve was out of the way, but by the time I got to it it was over the head and the patient had a traumatic neuritis for many months afterward. So it isn't always a simple task to remove some screws.

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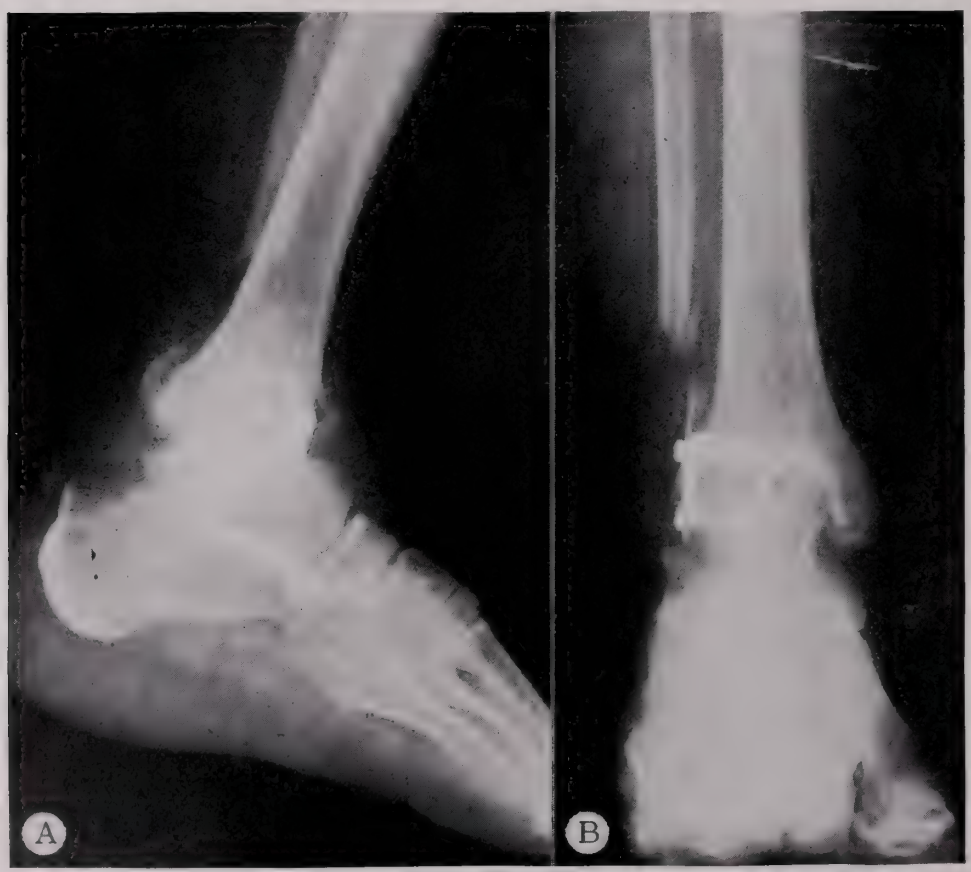


Fig. 5 (Case 2)—A and B, Appearance 11 days after Royal Air Force type of arthrodesis was performed.

Dr. Detenbeck:

Case 2 is that of a 58-year-old rabbi who fractured his right ankle in January 1966. He was treated by his local physician, who did an open reduction of the medial malleolus. Pain in this ankle joint was present postoperatively and continued until August 1967, when the screws were removed from the medial malleolus. This did not relieve his discomfort and he was seen here for evaluation in November 1967, almost two years after the original fracture. Roentgenograms at that time showed marked degenerative changes in the ankle and he was advised to have an ankle arthrodesis (Figure 4).

Dr. Bickel:

This looks as if he had not only the fracture you described but also some degree of tibiofibular diastasis. He seems to have some lateral shift of the talus. Again, Dr. Coventry, it looks like a broad talus, doesn't it? And the medial malleolus is better sized than in the first case, but the talus is broader than normal. I think I can see a modest shift of the talus to the outer side of the mortice. Disruption of the articular cartilage seems obvious. The patient has a marked limp and much ankle distress. Would anybody disagree with doing an arthrodesis?

Dr. Detenbeck:

On November 20, 1967, a modified Royal Air Force arthrodesis of the ankle was performed. This type of arthrodesis uses the distal part of the fibula as a graft to span the site of arthrodesis after freshening and alignment of the joint. Figure 5 shows internal fixation 11 days after the arthrodesis. A short leg cast was applied. Figure 6, taken after removal of the

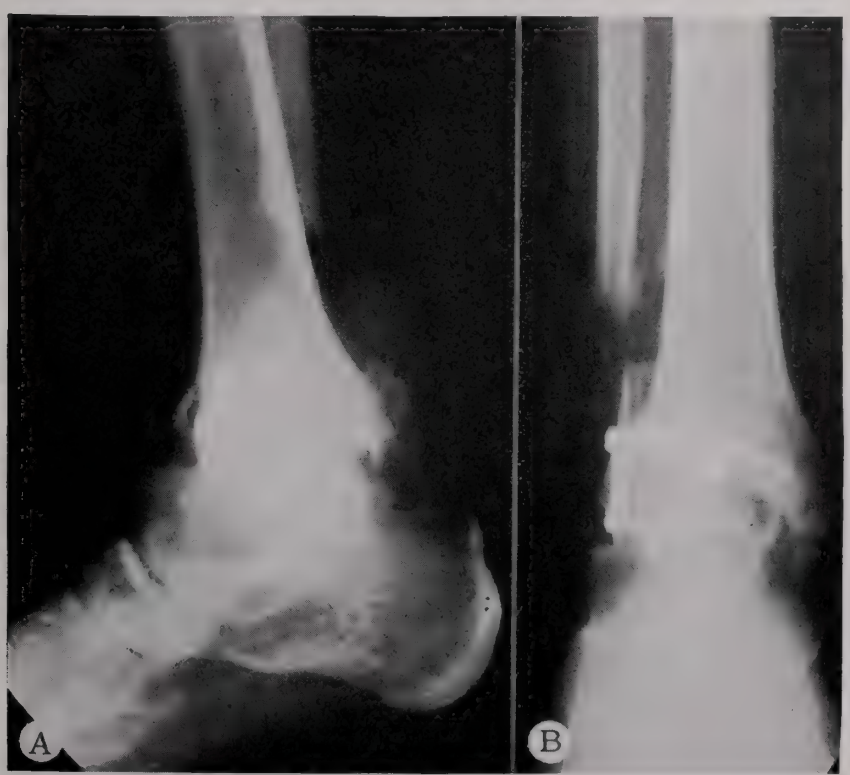


Fig. 6 (Case 2)—A and B, Appearance 4 months after Royal Air Force type of arthrodesis.

cast three and one-half months postoperatively, shows that the ankle apparently was solid. A double iron upright brace was applied.

Dr. Bickel:

Dr. Janes, would you care to comment on Royal Air Force fusions of the ankle? You have had more experience with them than anybody.

Dr. Janes:

I don't know too much about them. In the Royal Air Force we did use tibial bone instead of the fibula at times, because the tibial graft is better shaped than the fibula and also because not much of the fibula is left after it has been shaped. In short, a piece of tibia can be used instead of the fibula.

Dr. Richard S. Bryan:*

One can use the same approach as in this procedure when one employs a compression plate to promote fusion of the arthrodesis and uses the fibula as a graft in the same way.

Dr. Bickel:

Dr. Janes, it is my understanding that this type of arthrodesis was first used in the Royal Air Force for comminuted fractures of the talus without involvement of the subtalar joint. Is that right?

Dr. Janes:

That is true, but a tibiocalcaneal arthrodesis can also be done by this method.

Dr. Bickel:

Yes. A Royal Air Force fusion really applies to an ankle joint only, or is it an ankle joint plus a subtalar joint arthrodesis?

Dr. Janes:

Most of them are done for fracture of the talus involving the ankle joint.

Dr. Lowell F. A. Peterson:†

The Chuinard operation is done with the iliac graft. Chuinard performs compression arthrodesis by impacting an iliac graft into a mortice cut vertically across the anterior portion of the ankle joint.

Dr. Coventry:

Is the approach an anterior one?

Dr. L. Peterson:

Yes. The graft is driven firmly between the talus and the tibia. This operation does not require any remodeling of the articular surface of the talus.

Dr. Bickel:

He developed this arthrodesis, did he not, Dr. Peterson, for the child who needs an arthrodesed ankle but in whom he could hope to preserve the distal tibial epiphysis?

Dr. L. Peterson:

Yes. It has worked well in my hands. As I recall, in the series that Chuinard and colleagues reported they included a number of adults as well, and there were no instances of nonunion. It is a nice way of using a limited approach and not changing the contour of the ankle at all.

Dr. Bickel:

A prerequisite is that the ankle must not be deformed, because one cannot

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correct a deformity by doing an arthrodesis in the Chuinard fashion.

Dr. L. Peterson:

Yes, this is true; the procedure does not permit much correction of a deformity in a child.

Dr. Bickel:

In essence, one distracts the articular surface of the ankle, puts a wedge, or cookie, or block of iliac bone between the articular surfaces that have been freshened, and allows the soft tissues to contract and thus supply dynamic or physiologic compression. In other words, it's a type of compression arthrodesis which attempts, in a child, not to destroy the tibial epiphysis.

Dr. Coventry:

I think we have all used this idea specifically.

Dr. Patrick J. Kelly:*

We talk about compression in an arthrodesis of the ankle, but this is not really what we mean. We are trying to get the raw bone surfaces pulled together. The Charnley compression apparatus for the ankle works so well because it closely approximates the raw joint surfaces. A problem that I wonder about with a Royal Air Force fusion is one that I have seen. The surgeon tends to take off too much laterally and ends up with the talus tilted into a valgus position.

Dr. Coventry:

The same occurs with triple arthrodesis or anything else in a lateral approach. The surgeon is likely to remove more bone where he is working and less at the end of the osteotome. Is that what you mean, Dr. Kelly?

Dr. Kelly:

Well, one could get a little idea of it on the anteroposterior x-ray view.

Dr. Coventry:

The same with triple arthrodesis?

Dr. Kelly:

Yes, one could do a triple arthrodesis and end up with a valgus foot.

Dr. Einer W. Johnson, Jr.:†

This has been my problem and one of the reasons that I have had to forego doing Royal Air Force arthrodesis of the ankle—not because there is anything wrong with the procedure, but because I could not, as Dr. Coventry says, be fully confident that, at the end of the osteotome, I was not taking a piece of the posterior tibial nerve or the area of the posterior tibial tendon or something else. I like an anterior approach and, as Dr. Bianco brought up once when we talked this over, one cannot use compression across an ankle joint unless one osteotomizes both malleoli. It is rather hard for me to osteotomize the medial malleolus and remove enough of it so that it is not a factor in distraction, that is, not in the way of compression. It is hard for me to get to the medial malleolus from the lateral side. I like to do an ankle

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arthrodesis from the directly anterior approach so that I can see everything, including both malleoli, and can dissect around posteriorly and do everything I want to do within convenient reach. I am not criticizing the Royal Air Force procedure; I am just saying I cannot do it.

Dr. Bickel:

In defense of the Royal Air Force type of arthrodesis I would say that I not infrequently have made a medial incision and removed the malleolus so that I am not too far away from my work. Then I am able to get good medial displacement of the talus, obtain satisfactory approximation of the raw surfaces, and avoid any valgus position. Approximation, retention, and some compression can then be obtained with the use of large vitallium staples. I like the procedure.

Dr. L. Peterson:

My opinion is that leg length is somewhat of a problem and one does not want to shorten it any further. This is again an advantage of the Chuinard procedure, because it does not alter length at all.

Dr. Lipscomb:

Along that same line, a Galley subtalar arthrodesis works if there is little motion in the ankle joint. I think all these methods have their place, and one should pick the method for the condition that is present when the arthrodesis is done. Obviously, if the foot is severely deformed, it should be corrected before arthrodesis is performed.

Dr. Johnson:

How did this one turn out? Did he get along well after the ankle arthrodesis? Could he walk on a side hill without distress?

Dr. Detenbeck:

He did well. He had minimal distress walking on a side hill, and he could get around on flat surfaces without trouble.

Dr. Bickel:

In conclusion, these two complicated fractures involving the ankle joint demonstrate some important aspects of treatment. First, although swelling may be massive and may dictate use of a padded dressing after closed reduction, this type of a dressing is usually not able to maintain the reduction. A far better method is to apply a cast that is well molded and then is split to allow for swelling. Second, open reduction and internal fixation of the medial malleolus are needed to stabilize the other two malleoli in the event of a trimalleolar fracture. If comminution is not marked, this is a rewarding and usually easy surgical exercise. Third, no matter how adequate the reduction, severe injuries about the ankle joint often lead to degenerative joint changes that require arthrodesis.

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Einer W. Johnson, Jr., M.D.*
Rochester, Minnesota

*Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

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In the following case history a neglected callus led to a gas gangrene infection. Coupled with the diabetic neuropathy was an obstruction to the superficial femoral artery (Figure 1) which devascularized the foot to a certain extent, thus aiding the development of infection.

Case History

A 51-year-old female with a twenty-year history of diabetes developed a draining ulcer in a callus on the ball of her right foot. Two days prior to admission on November 20, 1964, she developed pain, swelling, and redness over the dorsum of the foot.

She was admitted to Swedish Hospital where she was found to be frebrile, with obvious crepitation over the foot. An x-ray showed gas formation. Cultures grew out E. coli and coagulase negative staphylococci. She was placed on large doses of penicillin and chloramphenicol and on November 21, 1964, an extensive debridement was carried out revealing black necrotic tissue.

During the first few postoperative days the general condition of the patient improved but the foot remained in jeopardy. An evaluation of the vascular status of the limb revealed no pulses palpable below the groin. A femoral arteriogram demonstrated a block in the superficial femoral artery but a good-sized popliteal artery with a two-vessel runoff. It was the opinion of the attending surgeon that without improvement in the vascular flow to the foot a below-knee amputation would be required.

On November 3, 1964, a saphenous vein shunt was fashioned to bypass the obstruction in the femoral artery. This was successful and a good pulsation was achieved in the posterior tibial artery at the ankle, with rapid improvement in the circulation of the foot making it possible to perform a transmetatarsal amputation on December 8, 1964.

Discussion

In this instance it was possible to salvage a mid-foot level of amputation in a situation that commonly results in the loss of a limb. The wound healed slowly but completely (Figure 2) and the patient was able to ambulate without difficulty by wearing a special shoe. This became important in her clinical progress, for renal and ophthalmic complications increased and she became essentially blind yet was able to continue to walk. She died of renal failure on March 21, 1967.

It may be asked whether it was not dangerous to perform the revascularization procedure in the face of an open and poorly healing wound. Yet in this

instance, the cellulitis had largely subsided and the administration of systemic antibiotics had cleared all but the immediate foot area of bacteria. Soon after the venous graft had been inserted the circulation of the wound improved, and after a few days it seemed feasible to perform the transmetatarsal amputation since a good posterior tibial pulse could be palpated at the ankle.

The distal foot amputation did not heal as promptly as is usually observed with a below-knee amputation, but healing was eventually complete and the wait was worthwhile, for the patient eventually lost her vision from diabetic retinopathy and ambulation with a higher amputation would have been

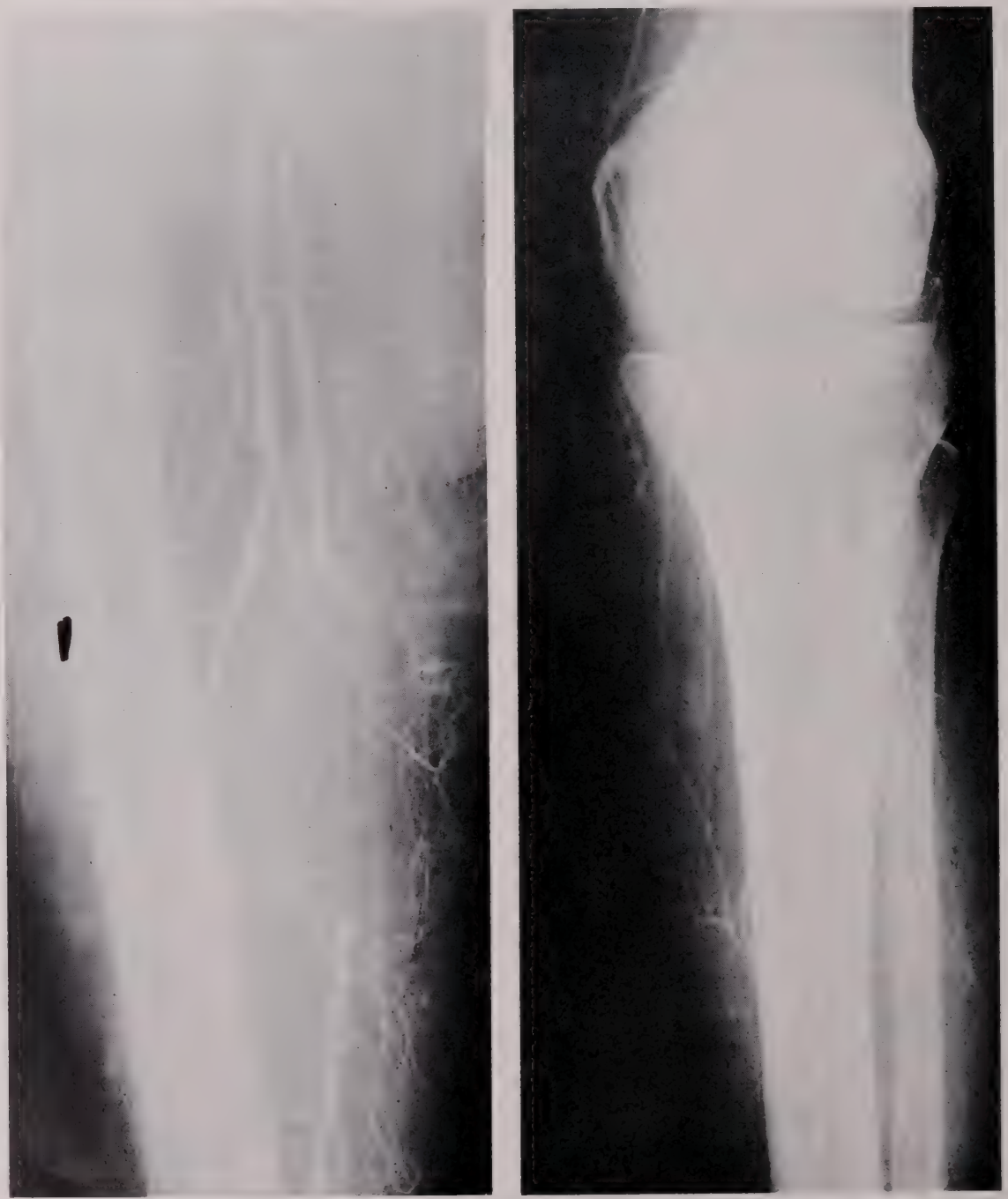


Fig. 1—Arteriogram revealing localized block in superficial femoral artery with good run off.



Fig. 2—Picture showing healed amputation.

much more difficult.

It would have been unthinkable to have inserted a prosthetic graft in this situation; consequently, if a usable vein were not available and the situation would not lend itself to a localized endarterectomy the revascularization procedure would have had to be foregone and a below-knee or above-knee amputation performed as the situation demanded.

The lesson to be learned in this case presentation is that although diabetics are prone to an endarterial disease they also develop arterial obstructive disease at levels that can be bypassed successfully by present-day vascular techniques. Diabetics with peripheral-vascular disease should not be excluded from complete evaluation and arteriograms, simply because they are diabetics.

The potential devastation that may be initiated in a diabetic from a simple callus or minor injury is once again illustrated. Proper and meticulous foot care by careful paring of calluses, the wearing of well fitting shoes, and vigorous treatment of infection should be routine in the physician's management of his diabetic patient.

Harrison H. Farley, M.D.
Minneapolis, Minnesota

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Warning: This drug is an analog of phenylbutazone; sensitive patients may be cross-reactive. If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Instances of severe bleeding have occurred. Persistent or severe dyspepsia may indicate peptic ulcer; perform upper gastrointestinal x-ray diagnostic tests if drug is continued. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy. Use with caution in the first trimester of pregnancy, and in patients with thyroid disease.

Precautions: Before prescribing, carefully select patients, avoiding those responsive to routine measures as well as contraindicated patients. Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patients should not exceed recommended dosage, should be closely supervised and should be warned to discontinue the drug and report immediately if fever, sore throat, or mouth lesions (symptoms of blood dyscrasia), sudden weight gain (water retention), skin reactions, black or tarry stools or other evidence of intestinal hemorrhage occur. Make complete blood counts at weekly intervals during early therapy and at 2-week intervals thereafter. Discontinue the drug immediately and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.

Adverse Reactions: The more common are nausea and edema. Swelling of the ankles or face may be minimized by withholding dietary salt, reduction in dosage or use of diuretics. In elderly patients and in those with hypertension, the drug should be discontinued with the appearance of edema. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. The patient should be instructed to take doses immediately after meals or with milk to minimize gastric upset. Drug rash occasionally occurs. If it does, promptly discontinue the drug. Agranulocytosis, exfoliative dermatitis, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), or a generalized allergic reaction similar to a serum sickness syndrome may occur and require permanent withdrawal of medication. Agranulocytosis can occur suddenly in spite of regular, repeated normal white counts. Stomatitis, salivary gland enlargement, vomiting, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported. While not definitely attributable to the drug, a causal relationship cannot be excluded. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, hypersensitivity angiitis, pericarditis and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.

Dosage in Osteoarthritis: Initial: 3 to 6 tablets daily in divided doses. Usually unnecessary to exceed 4 tablets daily. A trial period of one week is considered adequate to determine the therapeutic effect of the drug. Maintenance: Effective level often achieved with 1 or 2 tablets daily, should not exceed 4 tablets daily.

In selecting appropriate dosage in any specific case, consideration should be given to the patient's weight, general health, age and any other factors influencing drug response.

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Dermatology

Diabetes Mellitus Cutaneous Manifestations

CUTANEOUS ABNORMALITIES associated with diabetes mellitus are varied and classification is difficult. Some are generalized (bronzing); others are localized (mal perforant). A few disorders occur where diabetes may be suspected but cannot always be proved (necrobiosis lipoidica). These dermatoses should be kept in mind for they may provide a diagnostic clue.

General Changes

Cutaneous abnormalities in diabetics may be due to dehydration (dryness of the skin and mucous membranes). Dryness may be associated with scaling and pruritus. Itching sometimes occurs without dryness. When severe and prolonged, pruritus leads to excoriation, infection, and eczematization.

Disorders of pigmentation are also associated with diabetes. Three types occur: (1) diffuse bronzing similar to that in Addison's disease due to an increased supply of melanocyte stimulating hormone, and (2) xanthochromia resembling icterus as a result of decreased ability to convert carotene to vitamin A in the liver. Xanthochromia is most intense on the palms, soles, forehead, nasolabial grooves, behind the ears, and over the knuckles. It does not involve the scleras, thus differentiating it from jaundice. (3) Slate-blue pigmentation with hemochromatosis. Sometimes in the latter diffuse bronzing secondary to the deposition of melanin is associated.

Infection

Diabetics have increased susceptibility to both bacterial and fungal infections. Candidiasis is common in diabetics. It frequently involves the anogenital region, although other intertriginous areas and the oral cavity may be affected. Systemic involvement is rare, but when it occurs the prognosis is grave. Candidiasis may be the presenting complaint in a patient with chemically unproved diabetes. This is important. Once diabetes is controlled cutaneous candidiasis can be eradicated by use of various nystatin preparations. Amphotericin B intravenously has been employed in the treatment of the systemic form of the disease. It is seldom curative.

Furuncles and carbuncles occur frequently in diabetics. Control of diabetes plus specific measures directed toward the infection are usually effective. These lesions may recur in spite of adequate control of the underlying disorder.

Trophic Disturbances

Circulatory impairment may lead to recalcitrant ulcerations on the soles as well as the ankles. On the soles the process usually begins as a hyperkeratotic area on the ball of the foot. Later the lesion becomes soft, moist, and painful. Eventually an indolent, necrotic ulcer develops (mal perforant). Degenerative changes in nerve terminals may play a causative role.

Any ulcer, whether trophic or traumatic, may lead to gangrene in the

diabetic. Other factors include neglect of the feet, dermatophytosis, and other infections. Gangrene frequently involves the toes, though any part of the body can be affected. Treatment is both medical and surgical.

Xanthoma Diabeticorum

Hyperlipemia secondary to diabetes may be associated with xanthomas. The eruption is characterized by multiple, small, brownish-yellow papules, nodules, and plaques. The lesions occur in crops. At times the disorder causes intense pruritus resulting in excoriations. Extensor surfaces, palms, and soles are frequently affected. There is hyperlipemia, especially elevation of neutral fat. A cloudy serum results. The lipid and cholesterol values of the serum return to normal and the eruption usually disappears after the diabetes is controlled.

Acanthosis Nigricans

In this disorder there are hyperpigmented, verrucous plaques involving the axillas, neck, genital and submammary regions, or any of the large flexor surfaces. The association of acanthosis nigricans with internal malignancy has been stressed when onset is in adult life. The disorder can also be associated with various endocrinologic abnormalities including diabetes mellitus. Whether this association is primary or merely a result of obesity accompanying many of the endocrine disturbances is unknown.

Lipodystrophy and Lipoatrophy

A rare group of disorders characterized by disappearance of the subcutaneous fat is included here. Bony projections, muscles, and vessels become prominent. Progressive lipodystrophy usually has a cephalothoracic progression with cessation of the process at the iliums. An increased incidence of diabetes mellitus and hyperlipemia has been reported in the disorder. Lipoatrophic diabetes may or may not be related to progressive lipodystrophy. Lipodystrophy is generalized in this type of the disease. Hyperglycemia (resistant to insulin), hyperlipemia, and accumulation of fat in the liver with ensuing cirrhosis have also been observed.

Necrobiosis Lipoidica

This disorder is characterized by yellowish-red, irregular, round, or oval plaques with sharp borders. The central portion of the lesion is atrophic. Telangiectases occur peripherally. There may be scaling, and rarely ulceration. The lower legs are affected usually, although lesions may be present on the trunk and upper extremities. Necrobiosis lipoidica occurs in patients who have chemically proved diabetes mellitus. There are cases, however, in which the glucose tolerance test is normal. Histochemical studies usually show changes in these lesions similar to those in other diabetic microangiopathies. Treatment of the disorder is unsatisfactory.

Dermopathy

Localized pigmentary changes in diabetics have been reported recently. In these patients brown macules occur on the pretibial areas, varying in size from 1.0 to 3.0 cm in diameter. Atrophic areas may be associated. Pigmentation is apparently due to hemosiderin. Microangiopathy is present as in necrobiosis lipoidica.

Iatrogenic

The dermatologic complications arising from diabetic therapy are included here. Hypoglycemic sulfonamides may be associated with allergic reactions as well as an ill-defined paroxysmal vasomotor erythema. The former are most frequent and consist of pruritus, erythema, purpura, urticaria, and occasionally vesicles or bullae. The reactions may occur any time, but usually from one to three weeks following the institution of treatment. These reactions are probably allergic, although cutaneous tests have been unsatisfactory.

Complications arising from insulin therapy range from allergic reactions to lipodystrophies. The former are probably due to impurities, protamine, phenol, and zinc. The latter are more important and occur most frequently in adult women following injection of insulin. Their onset is usually within five years after treatment with insulin has been instituted. Lipodystrophy occurs in two forms: hypertrophic and atrophic. The hypertrophic type resembles lipoma microscopically. The lesions sometimes regress spontaneously or may undergo involution following infiltrations of hyaluronidase of hydrocortisone. The atrophic form occurs as depressed plaques varying in size from one to several centimeters. No spontaneous regression occurs in this type. Prophylactic measures are helpful (rotation of sites of injection).

Conclusion

The recognition of dermatoses associated with diabetes mellitus is important in the diagnosis of the disease as well as the so-called prediabetic state. Unfortunately, most of these manifestions are resistant to treatment.

Willard C. Peterson, Jr., M.D.*
Minneapolis, Minnesota

*Division of Dermatology, University of Minnesota Medical School, Minneapolis.

Greek vs. Christian

The Greek world exalted the healthy and sound and considered disease the sign of an inferior being. In the Christian world there was a definite tendency to glorify suffering and to look up to the sick and suffering man as to a superior being. Christ crucified, through his agony and death, had redeemed the world. Whoever suffered was carrying the Cross in the footsteps of his Master. Suffering was interpreted as an ordeal and whoever stood the test without rebellion could expect to be rewarded in the hereafter. The story of the righteous Job suffering unrighteously, rebelling but then humbling himself and submitting to God, acquired increased significance. In Christianity *Pathos* became *Ethos*. Suffering was a sign of grace, not to be evaded but sought.*

*Henry Sigerist, M.D.: Medicine and Human Welfare, 1941.

He and I have been dead these two years, but we don't choose to have it known.—Lord Chesterfield

---

Government is like a stomach; if it's doing its work right you will hardly realize you've got one.—Nuggets



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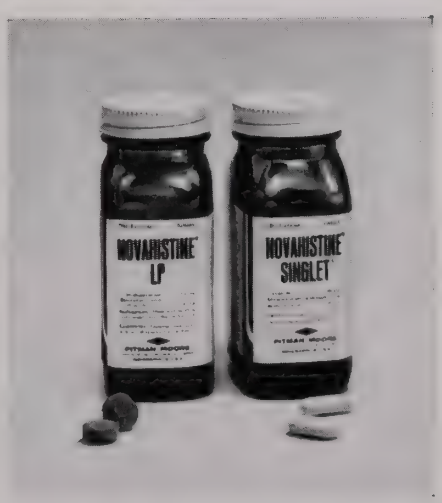
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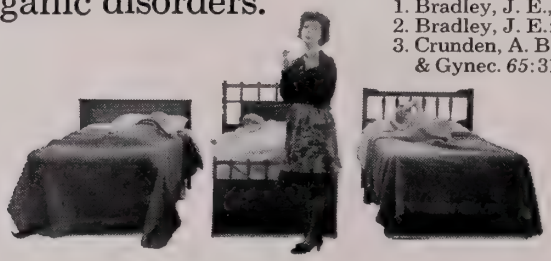
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1. Bradley, J. E., *et al.*: J. Pediat. *38*:41 (Jan.) 1951.
2. Bradley, J. E.: Mod. Med. *20*:71 (Oct. 15) 1952.
3. Crunden, A. B., Jr., and Davis, W. A.: Am. J. Obst. & Gynec. *65*:311 (Feb.) 1953.



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Precautions: Use may result in overgrowth of nonsusceptible organisms. Constant observation is essential. If new infections appear, take appropriate measures. Use of tetracycline during teeth development may cause discoloration of teeth.

Side Effects: Gastrointestinal system—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin—maculopapular and erythematous rashes (a case of exfoliative dermatitis has been reported); photosensitivity reaction, onycholysis and discoloration of nails (rare). Kidney—rise in BUN, apparently dose-related. Hypersensitivity reactions—urticaria, angioneurotic edema, anaphylaxis. In young infants, bulging fontanels have been reported following full therapeutic dosage. This symptom has disappeared rapidly when drug is discontinued. Teeth—dental staining (yellow-brown) in children of mothers given tetracycline during the latter half of pregnancy, and in children given the drug during the neonatal period, infancy and early childhood. Enamel hypoplasia has been seen in a few children. Blood—anemia, thrombocytopenic purpura, neutropenia, eosinophilia. Liver—cholestasis (rare), usually at high dosage. Tetracycline may form a stable calcium complex in bone-forming tissue. If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy.

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Clinical Path Conference

Diabetes and Infection

Calvin Bandt, M.D.:*

First Hospital Admission

A 64-YEAR-OLD white woman was admitted because of rectal bleeding. A rectal mass lesion was discovered and biopsied and found to be an infiltrating adenocarcinoma. Physical examination was otherwise normal except for obesity and a large ventral hernia. The patient had been known to have diabetes mellitus for some years, but this was reasonably well controlled with tolbutamide, 1.5 grams daily.

On the 15th hospital day the patient underwent an extensive combined abdominoperineal resection of the rectal carcinoma and the contiguous lymph nodes which were involved with the tumor. This operation included a panhysterectomy and total excision of the vagina as well as repair of the large ventral abdominal hernia.

Postoperative Infection

Her postoperative course was complicated by an extensive wound infection with coliform organisms; episodes of congestive heart failure, atrial arrhythmias and digitalis intoxication; the development of a persistent urinary tract infection with, at first, Aerobacter and subsequently Pseudomonas organisms; and at least one episode of apparent gram-negative septicemia. Incision, drainage and irrigation of the wound, with intensive antimicrobial chemotherapy (including courses of cephalothin, penicillin, chloramphenicol, streptomycin, nitrofurantoin, mandelamine, and colistin) finally succeeded in healing the surgical wound but failed to eradicate the urinary tract infection. Insulin was used to control her diabetes during the immediate operative interval, but thereafter tolbutamide was again instituted. Three weeks prior to her discharge, the patient developed a rather prolonged hypoglycemic reaction and the tolbutamide was withdrawn. It was not reinstituted.

Laboratory Studies

After 133 hospital days the patient was discharged. At that time her hemoglobin was 13.4 grams, her white blood count 19,500 with 85% neutrophils. Urinalysis disclosed a specific gravity of 1.010, 2+ albumin, a trace of sugar, occasional red blood cells and 200 white blood cells per high power field. Fasting blood glucose was 267, blood urea nitrogen was 40 mg% and serum electrolytes were normal. Urine culture produced over 100,000 colonies of Monilia, alpha streptococci, Proteus and approximately 50,000 colonies of Staphylococcus aureus and Pseudomonas. The Pseudomonas was sensitive only to colistin and polymixin B. The patient was given a prescription for mandelamine, 2 grams daily and vitamin capsules.

Second Hospital Admission

Four days after discharge the patient was admitted to the Neurology Service with coma and right-sided focal motor seizures. Because of hypotension she was given metaraminol 10 mg and lanatoside-C 0.8 mg in the ambulance en route to the hospital.

*Associate Pathologist, Hennepin County General Hospital, Minneapolis.

Admission physical examination revealed a blood pressure of 100/60, a pulse of 100 and irregular, respirations 30 and deep and full. The rectal temperature was 103 degrees. The patient was deeply stuporous, responding to painful stimuli with only slight movement in the extremities . Tendon reflexes were hypoactive. The Babinski sign was questionably positive on the right. Her breath was noted to be sweet. The abdominal wounds were open and draining material with an odor thought by the examiner to be characteristic of Pseudomonas. There was a new open, macerated lesion over the sacrum. The skin was dry, and bluish mottling was observed on the legs and arms. Lymphedema was present in both lower extremities. The lungs were found to be normal and the heart was normal except for frequent premature beats.

Laboratory Studies

The hemoglobin was 11.6, white blood count 33,200 with 93% neutrophils. Urinalysis showed a specific gravity of 1.012, 1+ albumin, 4+ sugar, red blood cells packed field, white blood cells packed field. The blood glucose was 1,182 mg%, BUN 113 mg%, blood pH 7.33, serum acetone positive, sodium 130 mEq.L, potassium 3.8 mEq/L, chloride 85 mEq/L, and CO_2 15 mEq/L. Culture of the urine disclosed over 100,000 colonies of a mixture of gram-negative rods including Proteus and Pseudomonas. These organisms as well as a coagulase positive Staphylococcus aureus were also recovered from the abdominal wound. Electrocardiogram was normal except for premature atrial and ventricular contractions. Chest roentgenogram disclosed no abnormalities.

Treatment

The patient was given an infusion of 1,000 cc of normal saline with 12.5 grams of mannitol, followed by 1,000 cc of dextrose in normal saline. Thereafter she was given continuous infusions of 5% dextrose in water with additional potassium chloride and sodium chloride. A summary of her fluid and electrolyte therapy is appended at the end of this protocol (Table). Fifty units of regular insulin was administered subcutaneously on admission, and she was given insulin according to her urine glucose in a dose of 20 units for 4+, 15 units for 3+, 10 units for 2+, and 5 units for 1+. One gram of chloramphenical was given immediately and thereafter 500 mg IM every eight hours.

TABLE

Fluid and Electrolyte Therapy

Hospital Day	Fluid	Electrolytes		Urine Output
1 (12 hours)	4000 cc	Mannitol	12.5 gm	2060
		KCl	140 meq	
		NaCl	300 meq	
2	4000 cc	KCl	56 meq	824
		NaCl	170 meq	
3	5400 cc	KCl	100 meq	875
		NaCl	350 meq	

Shortly after admission she was transferred to the Medicine Service, where this treatment program was continued. During the next 48 hours her level of consciousness improved slightly and she was observed to be moving in bed and moaning. No further seizures were observed. Twenty-four hours after admission urine glucose was negative although blood glucose at the same time was 500 mg%. Serum acetone became negative and remained so. The patient received 70 units of regular insulin on the first hospital day, 60 on the second and 55 on the third. On the third day serum sodium was 128 mEq/L, potassium 5.4, chloride 100, CO_2 16 mEq/L. BUN was 92 mg%. A lumbar puncture was performed and examination of the cerebral spinal fluid was normal.

Late on the third hospital day the patient was transferred to the Surgery Service. Little change in her condition was observed until 12 hours later when she abruptly developed respiratory distress and became hypotensive and "ashen" in color despite oxygen administration. Her blood pressure then became unobtainable and she ceased breathing. Resuscitation was unsuccessful. Blood cultures obtained on admission became positive for Pseudomonas on the day the patient died. An autopsy was performed.

Clinical Discussion

Robert Maslansky, M.D.:*

This protocol describes the course of events in over 100 days of hospitalization, and for all practical purposes I think the four-day absence may be disregarded. The entire course can be viewed as one hospital admission for a patient who comes in for treatment for carcinoma and ultimately dies. Among other pertinent facts is her dying a septic death. There were enough organisms in her to account for several foci of infection. Having said this we have to ask: where did this sepsis begin and where did it finally end? As for whence it came, I suspect that in a diabetic with this type of problem, the logical organ is the kidney, especially since we see in the earliest part of the protocol that she had regional lymph nodes involved with a virulent cancer. One wonders whether there might have been dissemination of this malignancy into the abdominal viscera and possibly metastases to her brain to account for the focal findings and lateralizing signs which were evident on the final admission. I must confess that I do not consider this a likely possibility, as it is improbable that this would occur so rapidly.

Diabetes and Arterial Disease

Now some thoughts about her diabetes. She is what has to be considered an insulin-dependent diabetic. We do not know how many years she has been diabetic, but I think it is fair to state that in diabetes over 20 years in duration, in spite of the age of onset, there is a one out of two chances of her having significant arterial degenerative disease, both in the small vessels, with retinal arteriole involvement, as well as in the medium-sized vessels, including the coronary arteries. I think the data from the literature supports this; and if we can assume this lady has been diabetic for some years, then we must assume that she has significant arterial disease. However, the dynamics of her diabetes changes appreciably when she becomes stressed, and she has undergone stress, first of all with her cancer (presumably by bleeding) and secondly with a major mutilative surgical procedure.

Diabetes and Surgery

I have a reference that is of some considerable interest to anyone who is considering operating on diabetics. It is the most definitive survey of diabetes in surgery that I know of: a study of 667 cases. I would like to read directly from the summary and conclusions. "A detailed analysis of the course of 487 diabetic patients who underwent 667 surgical procedures is presented. Twenty-three percent of the patients in the series were found to be diabetic either before surgery (100 instances) or during their surgical admission (12 instances). It is concluded that diabetes is frequently first discovered on the surgical services of general hospitals. Arteriosclerosis of all forms was present in thirty percent of the patients and accounted for twenty-nine percent of the deaths. Infection was the greatest hazard of the diabetic surgical patient, being the cause of eighty percent of the emergency operations, and accounting for eighty percent of the surgical complications and seventy-five percent of the nonsurgical complications. Ninety percent of the patients with diabetic nephropathy, who had surgery during the period of study, were beset with septic complications."† I think the salient point is that operating on a diabetic, insulin-dependent or independent, is considerably more risky than operating on a non-diabetic, particularly with regard to sepsis.

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†Galloway, J. A. and Shuman, C. R.: Diabetes and Surgery. Amer J Med 34:177, 1963.

*Clinical Assistant Professor of Medicine, University of Minnesota, Minneapolis.

Renal Disease

It is tempting to consider diabetic acidosis part of the patient's problem during her last days; however, I doubt that. What I think happened was that the kidney had simply given up fighting a life-long battle of acidosis. It was just not sufficiently there to provide the internal milieu with a buffer against the acidosis. What we are dealing with is doubtless renal acidosis.

This is borne out by a blood urea nitrogen of 113 mg%. The reason the kidneys failed is because they were missing some parts, namely, the papillae. This is a presumption on my part, but I think I am coming right to the heart of the problem when I say that I believe this patient had necrotizing renal papillitis, sometimes called renal medullary necrosis, though at no point in the protocol is it indicated that a definitive diagnostic test was done. Renal papillitis is a diagnosis readily arrived at in circumstances like this, if one can microscopically visualize papillae in the urine. This is usually most effectively done by having the urine strained through a piece of cheesecloth. On two occasions I have seen papillae in the urine when this was done. According to the literature on renal papillitis the papillae are sometimes missed because they are too small or fragmented.

Glucose Clearance

Lastly, with respect to renal lesions, one wonders about Kimmelstiel-Wilson's disease, perinephric abscess, or simple pyelonephritis. My impression from the protocol is that the flow of events was entirely too staccato. There was not simply a downhill course from the time of initial surgery to her death; rather there were periods of remission and exacerbation which terminated in the catalysmic event with the acidosis, azotemia and ventricular fibrillation. Now there is one little loose end I want to wrap up. That is the paradox of 500 mg% of sugar associated with no glycosuria. I do not know what happens to glucose clearance when the papillae are gone. I must confess that after some review I could find no literature on the subject. But my surmise is that the threshold goes up, and perhaps this is the circumstance that prevailed here: that though she had 500 mg% of sugar in the blood, the kidneys were just not clearing it.

I think this woman had necrotizing renal papillitis and that she was septic. I believe she had an adenocarcinoma of the rectum with metastases to the regional lymph nodes. In addition she had diabetes mellitus of the adult onset type; and she probably had a small amount of coronary artery disease, besides, along with cerebral arteriosclerotic degenerative disease. This is where I am going to stop.

Clinical Diagnoses

1. Diabetes mellitus of adult onset.
2. Necrotizing renal papillitis.
3. Sepsis
4. Metastatic adenocarcinoma of the rectum
5. Coronary and cerebral arteriosclerosis

Pathologic Findings

Dr. Bandt:

I will preface the pathological discussion by saying that we have a somewhat incomplete autopsy; we were excluded from examining the brain at

the request of the family. Consequently, the etiology of her neurologic problems which precipitated the final admission is not known.

External examination showed bilateral lower extremity edema and thrombosis of both saphenous veins. Both the abdominal and perineal wounds were opened and drained, with granulation tissue and no evidence of any lobulated abscess. The heart weighed 430 grams and was enlarged. The coronary arteries showed no significant coronary artery atherosclerosis; but on subsequent microscopic examinations there was moderate to severe involvement of the small coronary vessels. In addition, there was some patchy myocardial fibrosis.

Pulmonary Pathology

The left lung weighed 230 grams, the right lung 400 grams. The lung pathology was largely confined to the right lower lobe and particularly the posterior basal portion, which was very dense without crepitus and very hemorrhagic. Along one edge, the part lying in the costophrenic angle was very yellow and soft, with a fibrous membrane around the outside of this area which, on sectioning, contained material that appeared to be an abscess. In the segmental artery to this area of the lung there was found an organizing thrombus, and the microscopic sections of this vessel showed an already well organized thrombus which had partially recanalized. This thrombus is of some age and corresponds in time with the episode of thromboembolism earlier in her hospital course. The surrounding lung was very necrotic and showed a complete loss of cellular detail with no inflammatory infiltrate. However, near this infarct there is some inflammation representing a pneumonia: probably a Pseudomonas pneumonia in combination with the old resolving pulmonary infarct. The organism is in part presumptive and determined from the fact that she had Pseudomonas growing from her sputum.

Sections from the spleen and liver showed small calcified nodules measuring up to 1 mm in diameter; these are old granulomas, with the most likely etiology of histoplasmosis, which has become completely calcified. Section of the pancreas showed a moderate number of hyalinized or partially hyalinized islets, which are compatible with the type of hyalinization seen in the adult onset type of diabetes.

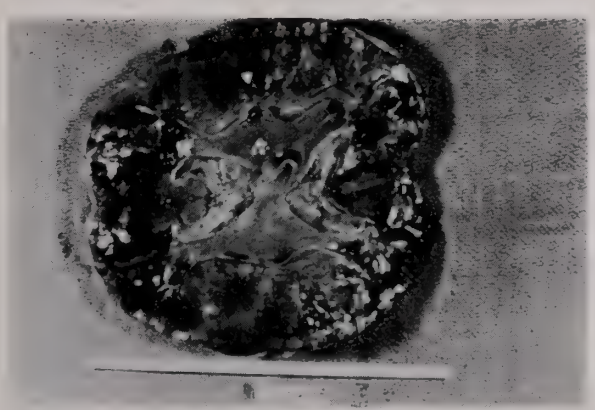


Fig. 1.—Kidney showing hemorrhage and infarction of papillae and pale areas of abscesses in cortex.

Kidney Pathology

The left kidney weighed 360 grams and the right 260 grams. Both pelvis and ureters were slightly dilated. The capsules stripped with difficulty and the cortex was very pale and soft. On section there were multiple pale yellow miliary areas throughout both the cortex and medulla. In addition, both kidneys showed a near total *loss of all the renal papillae* with necrosis of the remaining medullary portion near the papillae. As Dr. Maslansky said, this is the hallmark of necrotizing renal papillitis. Microscopic section through the remainder of one of these papillae shows that the parenchyma is completely necrotic. In addition, there are large masses of inflammatory cells, most of which are neutrophils, representing *small microabscesses* (Figure 1).

A Gram's stain done on this tissue showed numerous small organisms approximately the size of a red blood cell, with the typical budding forms of a yeast. These are a species of Candida, probably Candida albicans. In addition to the yeast forms, in other areas we were able to find the pseudohyphae form of the Candida organism. Other areas from the same block of tissue show large clumps of gram-positive cocci which are growing in clusters and appear to be Staphylococcus aureus. The gram-negative organisms which we presume to be there from the urine cultures and other data did not show up well enough on the Gram's stain for us to be able to say they were definitely there.

The glomeruli show early *intercapillary glomerulosclerosis* typical of diabetes mellitus; however, this is so minimal that it would not cause uremia by itself. This is supported by the fact that she had a normal BUN when first admitted. There also was some early hyalinization of afferent and efferent glomerular arterioles.

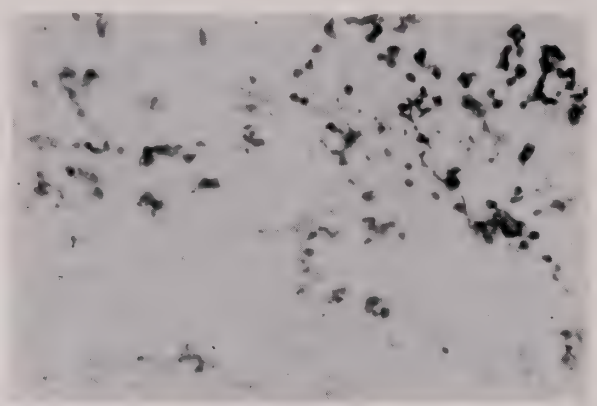


Fig. 2—Gram's stain (X430). From renal papilla, with necrotic material and pseudohyphae of Candida species.

Pseudomonas Septicemia

The relationship of the Pseudomonas septicemia to the necrotizing renal papillitis is still unclear. Normally Pseudomonas has very little talent for invasion and is usually seen in patients who are debilitated—with diabetes, burns, or lymphomas. Thus, the possibility that Pseudomonas is an agonal infection may be true in this case. The fact that she did not show gram-negative shock as a clinical picture is not too unusual, because Pseudomonas does not have the potential to produce gram-negative shock in the same manner that organisms such as Aerobacter and E. coli do. In only about 10% of the cases of Pseudomonas septicemia is there a true picture of gram-negative shock.

There is one other interesting aspect of Pseudomonas septicemia in that it has also been reported as causing a syndrome of disorientation, coma and convulsions. It is interesting to speculate that the Pseudomonas grown from her blood shortly after admission may have been the etiology of this. However, there is no proof.

Candida also has very little potential for invasion; but in debilitated patients such as diabetics it will cause true infection. I think this is the case here because we actually have true invasion of the tissue by the organism.

The etiology of necrotizing renal papillitis is not known, but it is usually associated with pyelonephritis. The organism may be quite variable and is not associated with a vasculitis. Part of the etiology in this case may have been the hydronephrosis which was evidenced by the dilated pelvis and ureters. Experimentally, ligature of the ureters and subsequent infection of the urine will produce a necrotizing papillitis in animals. This patient probably had this hydronephrosis as a result of her radical surgery with some injury to the terminal ureters, and this may have been contributory to the final outcome.

The portal of entry for the septicemia is unknown, but there were multiple sources with a pyelonephritis, pneumonia and wound infection.

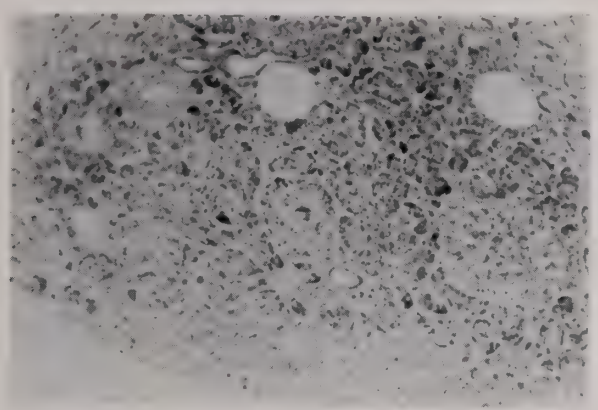


Fig. 3—Pancreas (X100). The islet in the center of the field has been largely replaced by hyaline material.

Pathological Diagnoses

1. Diabetes mellitus, adult type.
2. Bilateral necrotizing renal papillitis and pyelonephritis, probably due to Staphylococcus, Candida albicans and Pseudomonas.
3. Right lower lobe pneumonia probably due to Pseudomonas.
4. Resolving pulmonary infarct, right lower lobe.
5. Early intercapillary glomerulosclerosis.
6. Status postoperative for adenocarcinoma of the colon with no evidence of residual tumor.

Calvin Bandt, M.D.
Hennepin County General Hospital

Men will wrangle for religion; write for it; fight for it; die for it; anything but live for it.—Charles Colton

Nature to the Rescue

Appendicitis

The operations of Nature often seem very stupid. Even the despised tapeworm is congenitally better off than we are. Any segment below the head can be devoured or destroyed, and it can reproduce itself without the aid of an intellect. The snake throws its venom into us and we die; the snake lives to carry more venom. A mosquito jabs us with malaria, yellow fever, and perhaps other undiscovered death-dealing germs, and we die; the mosquito thrives on the deadly poison.

Yet, at other times, Nature will accomplish, unaided, cures more miraculous than any we have ever dreamed of. Frequently, in operating upon other organs of the abdomen, one will find that Nature has performed a surgical operation resulting in the cure of the most fatal type of appendicitis—the like of which is far beyond the power of man even to attempt. Georgia, a student at the University of Wisconsin, was brought to the hospital with an injury demanding surgical intervention. According to the usual routine, I looked for the appendix when I had completed my work in the abdomen. The appendix had left its location and had wandered off in the direction of the gall bladder. Tracing its course, I found it to be neatly enveloped in peritoneal tissue, which formed a canal ending in the intestine six inches from its beginning. It had taken a perfect short route, or bypass, from one intestine to another.

Neither she nor her parents could give me a typical history of a ruptured appendix, but they did remember that when she was quite young, during one of her stomach upsets, the doctor had thought she had colitis—a convenient term, which in those days usually meant ignorance of the true cause of illness. It was probably a ruptured appendix; and, in the face of a fulminating infection, Nature had burrowed—or, rather, constructed a canal toward a less vulnerable site—and had bored a hole through to the large intestine (more resistant to infection than the small intestine), thereby saving Georgia's life.*

*Joseph A. Jerger, M.D.: Doctor, Here's Your Hat!, 1939.

THE PERENNIAL PRONENESS

The respectable medical historian, Fielding H. Garrison, referred to a "fetishistic instinct," a "primitive craving for the supernatural which is ever latent in man." This craving he saw as a common aspect underlying primitive medicine and modern quackery . . . Rabbits' feet afford a steady market in America, at prices ranging from a dime to five dollars. Charms, voodoo bags, and love potions have been said to bring in a million dollars a year from residents of Alabama, Mississippi, and Louisiana alone. And a Missouri root doctor found customers for three magical remedies, a cathartic, an emetic, and—as he called the third—a "rank pizen," all made from the very same root. Hibobalorum was prepared by peeling the bark downward, Lobobahirum by peeling it upward, and Hi-lo-bustem by peeling it around.*

*James Harvey Young: The Medical Messiahs, 1967.

Thinking is more interesting than knowing, but less interesting than looking.
—Goethe

A once-popular treatment for back pains was to have the seventh son of a seventh son stand or walk on the patient's back.





The pain of earache was allegedly relieved by holding a hot roasted onion to the ear.

For headache, a sovereign remedy was to wear a snakeskin round one's head.



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Each tablet contains:
Codeine Phosphate gr. 1/2 (Warning—May be habit forming), Phenacetin gr. 2 1/2, Aspirin gr. 3 1/2, Caffeine gr. 1/2.

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New

Therapeutic breakthrough in non-narcotic control of the pain of

Tegretol®
carbamazepine

trigeminal neuralgia

Warning
Fatal cases of aplastic anemia have been reported following treatment with Tegretol. Agranulocytosis, thrombocytopenia and transitory leukopenia have also been observed.
Complete blood and platelet counts should be done prior to and at regular intervals during treatment with the drug (see recommendations under "Important Note and Precautions") to help in the early detection of serious bone marrow injury. Abnormalities in initial blood tests should rule out use of the drug. Also, patients should be made aware of such early toxic signs of a potential hematologic problem as fever, sore throat, mouth ulcers, easy bruising and petechial or purpuric hemorrhage. Should such signs appear, the patient should be advised to discontinue the drug and to report to the physician immediately.

Indication Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia. It is not a simple analgesic and should never be administered for relief of trivial facial aches or pains.
Contraindication Do not use in those with a known sensitivity to any tricyclic compound or in those being treated with M.A.O.I. agents. As long a period as possible should elapse before using Tegretol in patients who have been treated with M.A.O.I.'s, with a minimum of 7 days. In such cases, initial dosage should be low and the patient's reaction to gradual increments closely observed.
Important Note and Precautions Familiarity with the clinical symptoms which lead to an accurate diagnosis of true trigeminal neuralgia and with the complete prescribing information, careful patient selection, a thorough examination before treatment and close patient supervision throughout the treatment period are essential to the safe and effective use of this drug.
Where feasible, Tegretol should not be used in conjunction with any potent drug which may increase the possibility of toxic reactions.
In pregnancy, the drug should not be prescribed during the first trimester and thereafter only to patients in whom the clinical situation warrants the potential risk. It should not be administered to nursing mothers.
Patients with increased intraocular pressure should be closely observed during treatment with this drug because of its anticholinergic effect.
Because of the drug's relationship to other tricyclic compounds, the possibility of activation of latent psychosis and, in the elderly, of confusion or agitation, should be considered.
Dizziness and drowsiness may occur and patients should be cautioned about the hazards of operating machinery or automobiles and of engaging in other hazardous tasks.
Use cautiously in patients with a history of coronary artery disease, organic heart disease, congestive failure or liver disease.
Before initiating therapy, the following laboratory procedures should be performed:
1. Complete blood and platelet counts which, if abnormal, should rule out the use of the drug.
2. Baseline evaluations of liver function.

During treatment with Tegretol, the following laboratory procedures should be performed:
1. Complete blood and platelet counts should be done at intervals of one week during the first month of drug treatment, every two weeks during the second and third months, and at monthly intervals thereafter for as long as the patient is taking the drug. A trend toward a decreasing white blood cell count should suggest a dosage reduction and more frequent laboratory and clinical evaluations. Should this trend continue, the drug should be discontinued.
2. Liver function tests must be performed at regular intervals during treatment with this drug since liver damage may occur during therapy. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.
3. Periodic eye examinations, including slit-lamp, funduscopy and tonometry, are recommended for patients being treated with this drug since many phenothiazines and related drugs have been shown to cause eye changes.
4. Complete urinalysis and BUN should be done on patients treated with Tegretol because of observed renal dysfunction.

Adverse Reactions Dizziness, drowsiness, unsteadiness on the feet, nausea, vomiting, aplastic anemia, transitory leukopenia, agranulocytosis, eosinophilia, leukocytosis, thrombocytopenia, purpura, abnormalities in liver function tests, cholestatic and hepatocellular jaundice, urinary frequency, acute urinary retention, oliguria with elevated blood pressure, albuminuria, glycosuria, elevated BUN, microscopic deposits in the urine, impotence, disturbances of coordination, confusion, headache, fatigue, blurred vision, transient diplopia and oculomotor disturbances, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, nystagmus, tinnitus, paralysis and other symptoms of cerebral arterial insufficiency, pruritic and erythematous rashes, urticaria, Stevens-Johnson syndrome, photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, alopecia, diaphoresis, recurrence of thrombophlebitis, erythema multiforme and nodosum, aggravation of disseminated lupus erythematosus, gastric distress, abdominal pain, diarrhea, constipation, anorexia, dryness of the mouth and pharynx, glossitis, stomatitis, fever, chills, adenopathy, lymphadenopathy, aching joints and muscles, leg cramps, conjunctivitis, left ventricular failure, aggravation of hypertension, hypotension, syncope and collapse, edema, aggravation of coronary artery disease and congestive heart failure. (Whether these cardiovascular effects are drug-related is not known. However, some of these complications have resulted in fatalities.) The necessity for discontinuing the drug should be dictated by the gravity and severity of the adverse reactions.
Dosage and Administration The drug should always be taken with meals if possible.
Initial: One-half tablet (100 mg.) b.i.d. on the first day. Thereafter, the dose should be increased in one-half tablet (100 mg.) increments every 12 hours until freedom from pain is achieved. To relieve pain, between 200 mg. and 1200 mg. per 24 hours may be necessary.
Maintenance: Initial control of pain can be maintained in most patients with a dose of 400 mg. to 800 mg. daily. Maintenance doses may range between 200 mg. and 1200 mg. daily.
At least once every 3 months during treatment period attempts should be made to discontinue the drug or to reduce the dose to the minimum effective level.
Availability Round, white, single-scored tablets of 200 mg. in bottles of 100 and 1000. (B)46-820-A
For complete details, please see Prescribing Information.

Geigy Pharmaceuticals
Division of Geigy Chemical Corporation
Ardsley, New York 10502

Geigy

uncommon relief of uncommon pain



The Divorced Depressive: "Forty, Forgotten

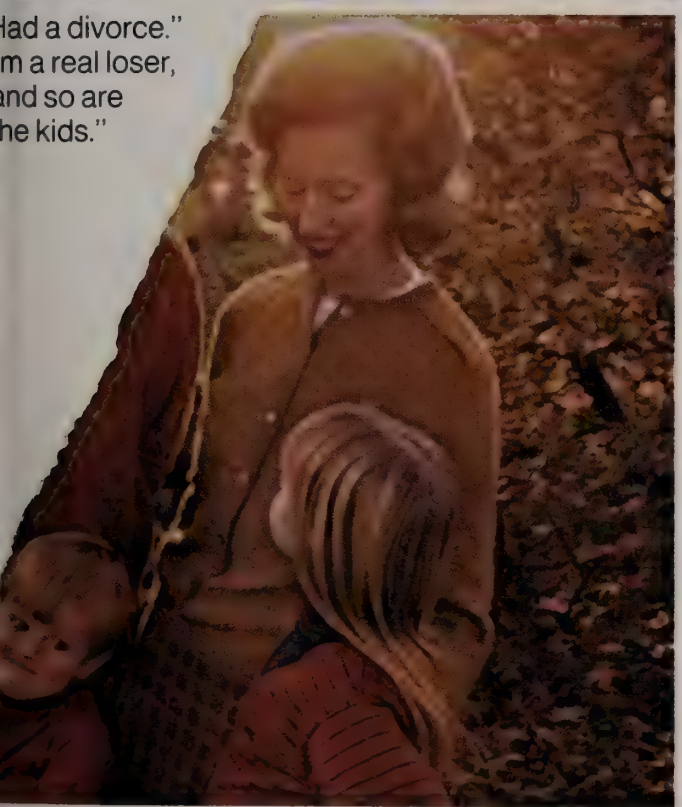
"Had a large wedding."
"Had a fine home and family."



TO-5757

.Forlorn"

Had a divorce."
m a real loser,
and so are
he kids."



The loss of marital compatibility results in nearly 500,000 U.S. divorces each year.

Depression characterized by untold guilt feelings, grief and loneliness may follow.

When you diagnose depression, Tofrānil may be indicated for relief.

As maintenance therapy during the active phase of depression, Tofrānil can often help prevent relapse.

The use of Tofrānil in patients receiving M.A.O.I.'s is contraindicated. In patients with cardiovascular disease, thyroid disorders, increased intraocular pressure; in those receiving anticholinergics (including antiparkinsonism agents), thyroid medication or antihypertensive adrenergic neuron-blocking agents; and in those in their first trimester of pregnancy—the special precautions listed in the Prescribing Information should be carefully observed.

Toxic reactions severe enough to require discontinuation of Tofrānil are uncommon. However, for complete details, please refer to the complete Prescribing Information.

Turn page for brief summary of Prescribing Information.

in depression

Tofrānil® imipramine hydrochloride

Geigy

in depression





Tofrānil® Geigy

imipramine
hydrochloride

Tofrānil®, imipramine hydrochloride
Indications: Tofrānil is recommended for the treatment of depressive states of diverse psychopathology.
Contraindications: The concomitant use of this agent and monoamine oxidase inhibiting (M.A.O.I.) compounds is contraindicated. Hyperpyretic crises or severe convulsive seizures may occur. Potentiation of adverse effects can be serious or even fatal. An interval of at least 7 days after M.A.O.I. therapy has been discontinued should be allowed before this drug may be substituted. Initial dosage should be low, increases should be gradual, and the patient's progress should be carefully observed.
Warning: Clinical reports have suggested that there may be a risk of teratogenesis associated with the use of this compound during the first trimester of pregnancy. Unless, in the opinion of the prescribing physician, the potential benefits outweigh the possible risks, it should not be used during the first trimester of pregnancy. Cardiovascular complications, including myocardial infarction and arrhythmias, have occasionally occurred in susceptible individuals. Patients with cardiovascular disease should be given the drug only under careful observation and in low dosage.
Precautions: Since suicide is always a possibility in severely depressed patients and one which may persist until significant remission occurs, such patients should be carefully supervised during early treatment. Some severely depressed patients may also require hospitalization and/or concomitant electroconvulsive therapy. Because of its anticholinergic effect, caution should be observed in prescribing the drug for patients with increased intraocular pressure.
In rare instances, transient cardiac arrhythmias have occurred in hyperthyroid patients and in patients receiving thyroid medication when this compound was added to the regimen. Imipramine may block the pharmacologic activity of guanethidine and other related adrenergic neuron-blocking agents.
The drug is not recommended at the present time in patients under 12 years of age.
Adverse Reactions: Dryness of the mouth, tachycardia, constipation, disturbances of accommodation, sweating, dizziness, weight gain, urinary frequency or retention, nausea and vomiting, peripheral neuritis, mild parkinson-like syndrome, tremors, rare cases of falling in elderly patients, confusional states (with such symptoms as hallucinations and disorientation), activation of psychosis in schizophrenics and agitation (including hypomanic and manic episodes) which may require dosage reduction and/or addition of a tranquilizer or temporary discontinuation of the drug, epileptiform seizures, orthostatic hypotension and substantial blood pressure fall in hypertensive patients, purpura, transient jaundice, bone marrow depression including agranulocytosis, sensitization and skin rash including photosensitization, eosinophilia, and mild withdrawal symptoms on sudden discontinuation after prolonged treatment with high doses. Occasional hormonal effects (impotence, decreased libido, and estrogenic effects) may be observed. Atropine-like effects may be more pronounced (e.g. paralytic ileus) in susceptible patients and in those using anticholinergic agents (including antiparkinsonism drugs).
Outpatient Adult Dosage: Initially, 75 mg. daily, increased, if necessary, to 150 or 200 mg. Maintenance dosage may be lower, 50 to 150 mg. daily, if possible.
Geriatric and Adolescent Dosage: Initially, 30 or 40 mg. daily, which may be increased according to response and tolerance. It is usually unnecessary to exceed 100 mg. daily.
A lag in therapeutic response, lasting from a few days to a few weeks, should be expected. When dosage recommendations are already being followed, increasing the dosage does not normally shorten this latency period and may increase the incidence of adverse reactions.
Availability: Round tablets of 25 and 50 mg.; triangular tablets of 10 mg. for geriatric and adolescent use; and ampuls, each containing 25 mg. in 2 cc. for I.M. administration.
(B)R-46-850-C

For complete details, please refer to the full Prescribing Information.

Geigy Pharmaceuticals
Division of Geigy Chemical Corporation
Ardsley, New York 10502

TO-6757



Grand Rounds

Some Aspects of Lipid Metabolism in Diabetes Mellitus

"Diabetes is a factor inherent in man and related to nutrition. Beyond this one can only speculate."—G. F. Cahill

RAFAEL CARMENA, M.D.
Minneapolis, Minnesota

CLASSICALLY, DIABETES MELLITUS has been considered to be a disturbance of the metabolism of carbohydrates consequent to a relative or absolute lack of insulin. It is well known that important disturbances of the metabolism of lipids—reflected by hyperketonemia and hyperlipidemia—are also present in this condition. As a matter of fact, elevated blood lipids in diabetes were known to Mariet in 1799[1] and Traill in 1823,[2] long before the discovery of the elevated blood sugar concentration by Ambrosiani[3] in 1835.

Hyperglycemia and glycosuria were immediately considered the cardinal signs of the disease and led to dietary treatment based on low carbohydrate. The hyperlipidemia did not cause obvious symptoms and was considered to be secondary to the carbohydrate disturbance.

Cawley in 1788[4] was apparently the first to associate diabetes with the pancreas based on autopsy findings. Attempts by several investigators to reproduce diabetes experimentally failed. In 1879 Langendorf[5] removed the pancreas of chickens and pigeons but the birds did not exhibit glycosuria or hyperglycemia. Mering and Minkowski in 1889[6] proved for the first time that dogs could be made diabetic by pancreatectomy. Minkowski also confirmed the observations of Langendorf in birds and concluded that herbivorous animals, unlike carnivorous ones, do not suffer from diabetes mellitus. The period between 1890 and 1921 saw a tremendous advance in the understanding of the intermediary metabolism of carbohydrates, culminating in the discovery of insulin by Banting and Best[7] in August 1921 and its clinical

*Presented as a Medical Grand Rounds at Hennepin County General Hospital, August 15, 1967.

I wish to express my gratitude to my adviser, Dr. Francisco Grande for allowing me the use of some of his unpublished material.

applications soon thereafter.

By contrast, the intermediary metabolism of lipids experienced a much slower development. Most of our knowledge has actually been acquired in the past two decades, paralleling the development of laboratory techniques. It is striking that until very recently the adipose tissue, some 15 kg. by weight in the average male and 20 in the female, was largely considered to be metabolically inert connective tissue filled with droplets of fat. It was particularly the work of Wertheimer and his associates[8] which proved that the adipose tissue not only has a very important metabolic activity represented by the high turnover of triglycerides, but it is also one of the principal target organs upon which insulin acts. This led the way to many important discoveries, among them the metabolic significance of the nonesterified fatty acids as an important transport form of energy.[9] It also focused attention on matters such as impaired lipid metabolism and atherosclerosis. Since vascular disease causes three fourths of diabetic deaths, it is not surprising that the metabolism of lipids in diabetes mellitus has been intensely investigated in the past few decades.

We shall review briefly some aspects of the alterations of serum lipids in diabetes mellitus with attention to nonesterified-fatty-acid metabolism in mammals and birds and its implications in the diabetic syndrome.

Disturbed Lipid Metabolism

Disturbances in lipid metabolism are an essential part of the deranged metabolism in diabetes mellitus. In the pre-insulin era, milky appearance of the blood due to accumulation of fat in the plasma was frequently seen in patients in diabetic ketosis and acidosis. It was considered to be a bad prognostic sign since it was associated with high mortality. However, its relationship to the metabolism of carbohydrates could not be established until insulin became available. With the use of insulin it was observed that the elevated plasma lipids of patients in diabetic acidosis experienced a sharp descent in very short periods of time. Some of the reported cases[10,11] had initial concentrations as high as 16.0 and 22.9 Gm. of total lipids per 100 ml. of plasma, and these values dropped in a few hours to normal limits after the administration of insulin. The existence of a direct correlation between serum lipid and blood sugar levels was also evidenced by the fact that adequate control of the carbohydrate metabolism resulted in marked reduction of all serum lipid levels.

In Controlled Diabetics

At present, investigators[12] agree that in carefully controlled diabetics there should be no significant elevation of the total blood lipids. However, the nonesterified fatty acids are increased even in well controlled diabetics, particularly if the plasma samples are taken before the morning injection of insulin. When the control of diabetes is not satisfactory, nonesterified fatty acids and triglycerides rise significantly. With very poor control, increases of cholesterol and phospholipids also appear and seem to be related to high incidence of vascular disease.[12]

The type of changes of serum lipids in diabetes seems to depend on the type, maturity or juvenile onset and the duration of the disease. Studies on juvenile insulin-dependent diabetics show a different pattern of lipid alterations than do studies done on maturity onset patients. In a recent publication,

Braunsteiner et al.[13] have investigated the relative body weight and the plasma nonesterified fatty acids, triglycerides, total cholesterol and phospholipids of 87 diabetics with ages ranging from 14 to 87. They were divided into four groups and compared with control groups of subjects of comparable ages with no evidence of metabolic disease. Group I consisted of 12 recently diagnosed diabetics without treatment or ketoacidosis. They found the nonesterified fatty acid and triglyceride fractions to be significantly elevated when compared to the control group. In Group II, 40 well controlled diabetics treated with insulin were studied. The serum cholesterol and phospholipid values were higher than in the control group, and triglycerides and nonesterified fatty acids were significantly elevated. Group III included 30 well controlled diabetics treated with Tolbutamide. The relative body weight was significantly higher than in the control group. The only lipid fraction significantly elevated were the triglycerides. Group IV consisted of five diabetics in ketoacidosis. The nonesterified fatty acids were very significantly increased, with 57% elevation in respect to the control group. The triglycerides also rose. In summary, the most striking differences were found in the concentration of triglycerides and nonesterified fatty acids. Serum triglycerides were elevated in all groups of diabetics. Nonesterified fatty acids were significantly elevated in patients with ketoacidosis and rose also in Groups I and II. An increased concentration of cholesterol or phospholipids was found only in well controlled diabetics treated with insulin. The relative body weight was significantly elevated only in Group III.

In Juvenile Diabetics

There is disagreement in the literature concerning the lipid alterations in juvenile diabetics. Some authors[14,15] have reported no significant changes in serum triglycerides in juvenile diabetics, while others[16,17] have found elevated triglyceride levels, especially in cases with angiopathy. In a recent publication, Hiekkala et al.[18] report on plasma lipids in 149 juvenile insulin-treated diabetics with ages ranging from five to 22 years, whose diabetes had been present for from a few months to 16 years. They have also studied the incidence of angiopathy among the patients as evidenced by the presence of retinopathy and/or nephropathy. Angiopathy was diagnosed in 40 cases, with a duration of diabetes of more than seven years in all of them. Serum cholesterol and phospholipids were found to be significantly elevated in all patients with angiopathy, who were also those with poorer control (high glucose spilling, ketosis and hypoglycemic reactions). In patients with no sign of angiopathy, increase in age or in the duration of the disease did not seem to influence the plasma cholesterol values. Total lipid values were significantly increased in the poorly controlled patients, in cases with duration of diabetes for more than 15 years and in connection with vascular disease. Similar results were also reported by Adlersberg[19] and Larson.[20]

Bahl and Bahl[21] have studied the serum lipids in a group of 75 diabetics in India. Their results showed significant increase in serum cholesterol concentration in 51 cases where vascular disease was diagnosed. Total lipid values were also found to be elevated in the same cases.

In Fasting Samples

Carlson[22] has investigated the concentrations of cholesterol and triglycerides in fasting serum samples and their relationship to the diabetic state.

There was no difference in cholesterol concentration between the patients and normal persons. On the other hand, the triglycerides were significantly increased above the normal level. The studies of Carlson show that the degree of control of carbohydrate metabolism exerts direct influence on the triglycerides. When diabetics are kept under good control (fasting blood sugar below 200 mg % and less than 15 Gm. of sugar in 24 hours' urine) their serum triglyceride values approach those of the control group. In a group of 20 patients with mild ketonuria without acidosis the blood sugar decreased on the average 60 mg % and the triglycerides 100 mg % after insulin was administered. No significant cholesterol changes were seen, probably because of the low turnover rate of cholesterol.

A summary of the present state of our knowledge about the plasma lipids during the course of the diabetic syndrome is presented in the Table, modified from Carlson. The nonesterified fatty acids and triglycerides are elevated from the beginning and can be reduced by treatment but not completely normalized. In the event of ketosis, these two lipid fractions rise markedly, and in the most exaggerated state even cholesterol and phospholipids will increase. When retinopathy or coronary artery disease appears, serum cholesterol is also elevated. In the Kimmelstiel-Wilson syndrome, the fraction that shows the most significant increase is the triglycerides.

Adipose Tissue Metabolism in Mammals and Birds

Adipose tissue is found in all homeotherm animals.[23] It has been said[24] that if animals were to exist without the convenience afforded by the adipose tissue it would be necessary to adjust the rate of absorption of food from the gastrointestinal tract to accommodate different rates of energy expenditure. The mammalian fetus shows a remarkable absence of depot lipids during intrauterine life, because the fetus is continuously fed through the maternal circulation. In post-natal life, animals are intermittent eaters and are con-

TABLE

Course of Diabetes	PLASMA LIPIDS		
	NEFA	Triglycerides	Cholesterol Phospholipids
Discovery	+ +	+ +	0
Clinical Control	+	+	0
Ketosis	+ + +	+ + +	0
Keto-Acidosis	+ + +	+ + +	+ +
Vascular Disease	+	+	+ + +
Nephropathy	±	+ + +	+ +

Modified from Carlson, L. A.

fronted with the problem of surviving during the fasting periods. Therefor they have to store temporarily much of the chemical energy ingested as food. This is done by lipogenesis and storing of fat in the adipose tissue.

There are several reasons for fat to be the preferred storage material: (a) it takes up less volume and weighs less per calorie of stored chemical energy than either carbohydrate or protein; (b) the body has, perhaps unfortunately, an almost infinite capacity to store fat, in contrast to its very limited capacity to store carbohydrate and protein.

Fat is stored in the adipose tissue as triglycerides, which constitute the major storage form of oxidizable substrate in mammals. There are three main precursors of adipose tissue triglycerides: (a) *nonesterified fatty acids,* demonstrated[25] but not considered to be a major one; (b) *triglycerides,* carried in chylomicrons and low density lipoproteins[25] which are for the most part broken down to glycerol and nonesterified fatty acids and resynthesized again to triglyceride (there is also evidence[26] that they can be taken up by the adipose tissue by pyocytosis); (c) *glucose,* the primary precursor of glycerol for adipose tissue triglycerides. If insulin is available, glucose enters the adipose tissue cells, is phosphorylated to glucose-6-phosphate and follows either the catabolic pathway, leading to triose-phosphate formation, or the anabolic pathway, leading to glycogen. The triose-phosphate pathway leads to the formation of glycerol-phosphate and acetyl-coenzyme A at a later step. It is important that the adipose tissue cells lack glycerol-kinase[27] and are not able to form glycerol-phosphate from free glycerol. The glycerol-phosphate necessary for triglyceride synthesis is derived only from glucose The synthesis of fatty acids requires acetyl-coenzyme A and triphosphopyridine nucleotide, reduced form and both are also derived from the catabolism of glucose.

By using glucose-C^{14}[28] it has been estimated that at a blood glucose of 90 mg % the adipose tissue utilizes 44% of it to form glycerol-phosphate; 42% goes to carbon dioxide, 13% to fatty acids and 1% to glycogen. The mobilization of fat from the adipose tissue occurs exclusively in the form of nonesterified fatty acid.[29] Nonesterified fatty acids are the only output form of adipose tissue triglycerides, in contrast to the multiplicity of modes of input.

Lipolysis and lipogenesis are under the control of neural, metabolic and hormonal factors. We shall review them briefly in normal and diabetic mammals, adding some comments on recent investigations on birds.

Neural Mechanism

The neural mechanism controls instantaneous delivery of fuel by the adipose tissue. It is mediated through the sympathetic system in which the adipose tissue is richly innervated.[30] Several investigators[31,32,33] have reported that the plasma nonesterified fatty acids in animals and man are decreased after the administration of ganglionic or adrenergic blocking agents. Bogdonoff et al.[34] showed that sympathetic discharge associated with emotional stress can elevate plasma nonesterified fatty acids in man.

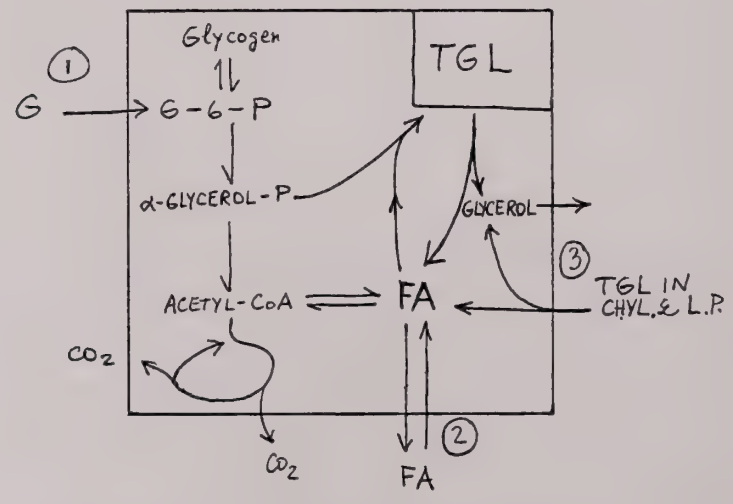
Metabolic Regulation

The metabolic regulation has also been called "glucose-cum-insulin."[29] The amount of glucose utilization is the main determining factor with respect to the net lipolysis and lipogenesis. When glucose utilization is low (starvation, diabetes) lipolysis exceeds lipogenesis and nonesterified-fatty-acid concentra-

tion in serum rises. Conversely, with excessive insulin and consequent increased glucose utilization, lipogenesis is also increased and nonesterified fatty acids are reincorporated into triglyceride. The explanation of these changes lies in the formation of glycerol-phosphate. Lipolysis continues to take place even at steady state,[35] and in order to maintain the depot fat constant lipogenesis must also be operating. For lipogenesis to occur, glycerol-phosphate has to be available. The only important source of it is the blood glucose. When glucose is not available the glycerol-phosphate requirements are not met and lipogenesis is shut off. The nonesterified fatty acids liberated by lipolysis cannot be re-esterified. They will leave the adipose tissue cell, become bound to albumin and circulate in that manner through the blood stream (Figure 1).

The nonesterified fatty acids are taken up by the tissues and converted to fatty-acetyl-CoA which may then be stored as triglyceride or oxidized to acetyl-CoA, which is converted into citric acid and finally oxidized to CO_2 and water. With the exception of the brain, all tissues are well equipped with enzyme systems for direct oxidation of fatty acids.[36] The skeletal and heart muscles take up most of the circulating nonesterified fatty acids to derive their energy. The liver also takes up nonesterified fatty acids and incorporates them into lipoproteins. When the mobilization of fat reaches high values, the liver's ability to cope with the nonesterified-fatty-acid load is exceeded and deposition of fat in the liver takes place.[29] Under normal circumstances, the half-life time for nonesterified fatty acids in plasma is two to four minutes.[37] If the plasma concentration of nonesterified fatty acids is normally around 600 micro Eq/L and the plasma volume 3 L, the flux of nonesterified fatty acids through the plasma in 24 hours would account for 160 Gm. of fat, about 60% of the daily energy production in man.[36]

The two major fuels for oxidation in mammals are glucose and nonesterified fatty acids. It was only logical to assume an interaction between the metabolism of fatty acids and that of glucose. This was postulated by Randle et



G = Glucose
FA = Fatty Acids
L.P. = Lipoprotein
TGL = Triglycerides
Chyl = Chylomicron

Figure 1

al.[38,39] some years ago and named the "glucose-fatty-acid cycle," the essential features of which are: (a) nonesterified fatty acids release from adipose tissue is inhibited by the uptake of glucose by that tissue; (b) glucose utilization by muscle is decreased by nonesterified fatty acids. The cycle provides a mechanism which, independently of hormonal control, will maintain constant plasma-glucose concentration (Figure 2).

Hormonal Control

The hormonal control is carried out by two different types of action. (a) *Lipogenetic hormones:* The work of Dole[40,41] showed that insulin causes the plasma nonesterified fatty acids to fall sharply. More recent work[42] has proved that insulin lowers the intracellular level of cyclic adenosine monophosphate (AMP) in adipose tissue. The action of insulin can thus be explained as decreasing the release of nonesterified fatty acids from adipose tissue, without affecting the rate of removal from blood. Some recent reports by Böhle[43] and Bergstrom[44] have shown that the prostaglandins can also inhibit lipolysis by blocking the formation of cyclic adenosine monophosphate. (b) *Adipokinetic hormones*: Many hormones have been shown to enhance lipid mobilization, some directly and others by permissive action. Epinephrine and norepinephrine are the most important adipokinetic hormones in mammals. Their action takes place through increased formation of cyclic adenosine monophosphate, which in turn activates the triglyceride lipase.[45] Some authors believe that the action of these hormones is also dependent on activation of the phosphorylases.[35]

Other adipokinetic hormones are somatotropic hormones, adrenocorticotrophic hormones, thyroid-stimulating hormones, thyroxine, adrenal corticoids, follicle-stimulating hormones, glucagon, some pituitary extracts like "frac-

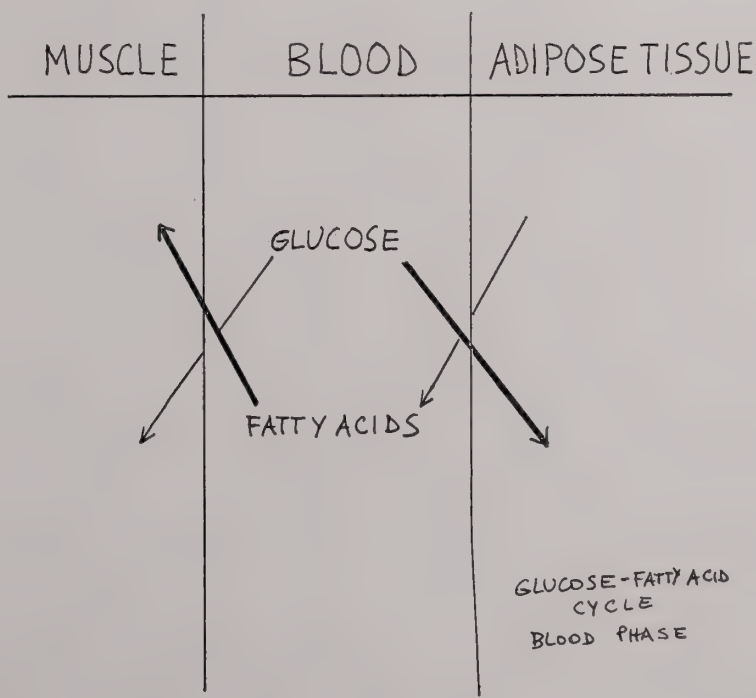


Figure 2

tion H," "peptide I" of Astwood, the "lipid mobilizing factor" of Sefter, the adipokinetic substance found in the urine of fasted normal humans and in that of diabetics.[46] Most of these substances act by favoring the formation of cyclic adenosine monophosphate. Others (adrenal corticoids) have a permissive action and potentiate the effect of epinephrine. However, adrenocortical hormones can, at high concentrations, have a direct effect on nonesterified fatty acid release.[47]

In birds, the recent work done by Grande has proved that epinephrine has no action on fat mobilization from adipose tissue. By constrast, glucagon seems to be the most potent adipokinetic hormone in these animals (duck, goose and rooster.) Moreover, Grande has also shown that in birds insulin does not prevent the mobilization of nonesterified fatty acids induced by glucagon. The administration of insulin at doses which produced a marked decrease of blood sugar did not decrease plasma nonesterified-fatty-acid concentration in birds. The same dose given to mammals caused a marked decrease of plasma nonesterified fatty acids.

Adipose Tissue Metabolism in Diabetes Mellitus

The alterations present in the adipose tissue of diabetic patients can be summarized as: (1) decreased glucose utilization, (2) increased release of nonesterified fatty acids to the blood and (3) decreased uptake of trigylcerides from the blood. These changes represent the increased lipid mobilization that occurs in clinical[48] and experimental diabetes.[41] It has been suggested[38] that part of the disturbances of carbohydrate metabolism characteristic of the diabetic state are not a direct consequence of insulin lack but a result of the increased mobilization and utilization of nonesterified fatty acids. As experiments in animals have shown,[53] complete removal of the pancreas is immediately followed by rise in plasma nonesterified fatty acids. This alteration precedes the elevation of the blood sugar.

In their "glucose-fatty acid cycle," Randle et al.[38] postulated that the increase in plasma nonesterified-fatty-acid concentration causes increased nonesterified-fatty-acid utilization by the muscle. This leads to decreased glucose utilization and in turn results in decreased sensitivity to insulin. This theory could provide a reasonable explanation for many unexplained features of human diabetes. According to Randle (Figure 3), the sequence of events in early diabetes might be as follows: (1) The breakdown of glycerides in the adipose tissue and muscle is increased with fasting in spite of a normal or raised plasma level of insulin. (2) After food ingestion, insulin in plasma rises higher and so does blood glucose, resulting in inhibition of the lipolysis in the adipose tissue but not in the muscle, where insulin does not affect glyceride breakdown. (3) Since plasma glucose and insulin are high, uptake of glucose by the adipose tissue is also very high, resulting in increased lipogenesis and deposition of large amounts of triglyceride in the adipose tissue. (4) Lipolysis in the adipose tissue is shut off. Nonesterified-fatty-acid levels in plasma will decrease and this will allow the entrance of blood glucose in the muscle. The immediate result is a fall in blood glucose levels, and in some cases hypoglycemic values may be reached, as in some diabetics, two to three hours after meals. (5) The fall in blood glucose causes the insulin level to decline, and lipolysis in the adipose tissue begins. Nonesterified-fatty-acid concentration in plasma will rise again and the cycle will proceed. The evolution from prediabetes to diabetes will appear when the pancreas is un-

able to respond to the increased insulin requirements.[52] The elevation of the fasting blood sugar level will be the immediate consequence.

Other investigators have supported Randle's theory with experimental evidence in vitro.[49] The adipose tissue from diabetic patients and from animals with experimental diabetes has been shown to release nonesterified fatty acid and glycerol at a higher rate than the corresponding normal tissue.

There are also studies done in vivo supporting that theory. Delorme[50] studied in the dog the effect of insulin injections on blood glucose at two different levels of plasma nonesterified fatty acids. When plasma nonesterified fatty acids were raised by a previous infusion of norepinephrine, the fall in blood glucose after insulin injection was significantly less than when nonesterified-fatty-acid concentration in plasma was kept normal. However, the results are questionable because of the use of norepinephrine.

Schalch and Kipnis[51] have studied in man the carbohydrate tolerance after an acute and sustained elevation of nonesterified fatty acids. In order to avoid endocrine or nutritional influences, nonesterified-fatty-acid levels in plasma were raised by the ingestion of 60 Gm. of emulsified corn oil followed in three hours by 50 mg. of heparin intravenously. The carbohydrate tolerance was measured with intravenous injection over four minutes of 25 Gm. of glucose. They studied 12 normal subjects and five patients with diabetes mellitus controlled on diet alone. Their results indicate that in man an elevation of plasma nonesterified-fatty-acid concentration may be associated with an impaired glucose tolerance and decreased target organ sensitivity to insulin. The degree of impairment in carbohydrate tolerance was found to be in direct correlation with the elevation of the plasma nonesterified-fatty-acid level.

Felber et al.[52] have investigated also the correlation between plasma nonesterified-fatty-acid values and glucose tolerance. They measured the carbohydrate tolerance in a group of normal subjects by ingestion of 100 Gm.

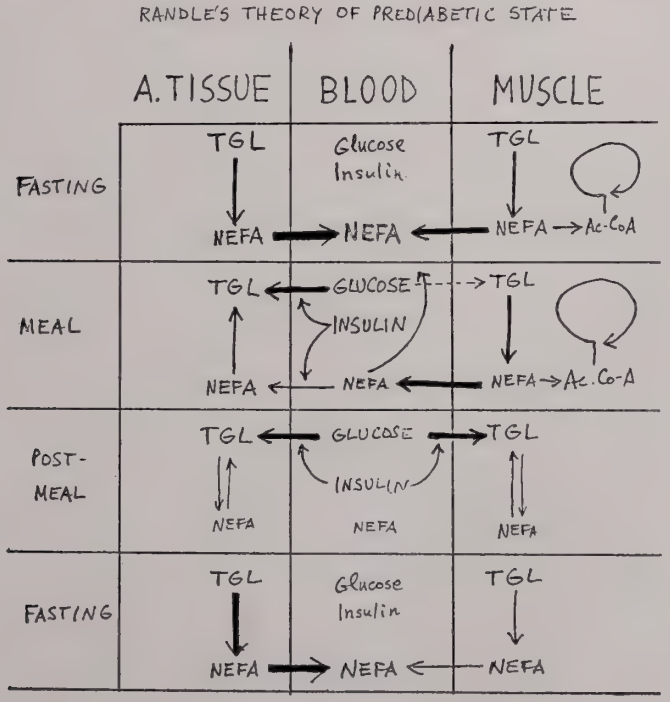


Figure 3

of glucose. The plasma nonesterified fatty acids were raised by ingestion of an emulsion of neutral fat and the glucose tolerance test was repeated. All subjects showed impaired glucose tolerance. These authors also studied the glucose tolerance of 13 obese subjects as compared with a group of normal people. The obese had elevated plasma nonesterified-fatty-acid value at fasting and showed a significant impairment of the glucose tolerance.

The effect of a low calorie diet on plasma nonesterified-fatty-acid level and glucose tolerance has been studied by Stowers et al.[54] They maintained a group of 15 severely obese subjects on a 2,500-calorie diet and measured their carbohydrate tolerance with intravenous and oral administration of glucose. The subjects were then switched to a 600-calorie diet, which caused a significant elevation of their plasma nonesterified fatty acid. The repetition of the carbohydrate tolerance test showed a significant impairment of the glucose tolerance, which was directly correlated to the elevation of nonesterified fatty acids.

Summary

In summary, elevation of plasma nonesterified-fatty-acid levels, whether present spontaneously or artificially provoked, is associated with a lower tolerance to carbohydrates. There are indications that this could be the first metabolic derangement leading to diabetes mellitus. The failure of pancreatectomy to produce diabetes mellitus in some avian species could be due to the fact that insulin does not prevent the mobilization of nonesterified fatty acids in these animals. According to Grande, pancreatectomized birds do not develop diabetes mellitus because their nonesterified-fatty-acid levels do not rise after pancreatectomy, as they do in mammals. If birds can be made diabetic by artificial elevation of the nonesterified-fatty-acid concentration, the hypothesis of Grande will receive full support. The theory that elevation of nonesterified fatty acids is an important first step in the development of the diabetic disturbance will be also further supported. This would considerably advance our understanding of the complex mechanisms responsible for initiating diabetes mellitus in man. Diabetes mellitus could be initially an essential metabolic disturbance becoming secondarily an endocrine disturbance.[52]

In the clinical field, impairment of glucose tolerance in the presence of high plasma nonesterified-fatty-acid values could become a very practical tool in the detection of pre-diabetics. Subjects responding to glucose tolerance tests with values in the border limits of normality will show marked impairment of their carbohydrate tolerance if their plasma nonesterified fatty acids are elevated prior to the test. We believe the data we have reviewed fully support the theory that alterations in lipid metabolism are a very important part of the complex metabolic alterations present in diabetes mellitus. The idea that a diabetic is "well controlled" because sugar-spilling, fasting blood sugar and ketonuria are low or absent should be modified. Plasma levels of nonesterified fatty acids, triglycerides, cholesterol and phospholipids should also be included among the routine laboratory tests for the detection and control of diabetes mellitus, and their values should be kept as close to normal as possible. This will probably result in a lower incidence of vascular complications in diabetics.

Case Report

A 54-year-old white female was admitted for the first time to Hennepin County General

Hospital on August 28, 1964, because of acute cellulitis of the left foot. The patient had been in good health until four days after admission, when she injured her foot on a piece of glass.

P. H. In May, 1964, she was treated at the Emergency Room for an indolent infected laceration of the right leg. Since that time she noticed increased frequency of urination, nocturia and increase in appetite.

F. H. No diabetes, tuberculosis or cancer. Mother died age 24 of acute appendicitis. Father died age 74 of heart attack. One sister had hypoglycemia.

S. H. Married, no children, works as cleaning lady in office building.

Positive Findings

Obese white female with an acutely swollen and tender left foot. Blood pressure 140/80; pulse 112, regular; temperature 101°.

Eyes: Right fundus showed microaneurysms and scattered exudate.

Extremities: Left foot swollen, erythematous and warm.

Laboratory Data

Hemoglobin 11.7; white blood count 19,200; fasting blood sugar 261 and 400 the following day; urinalysis: 3+ glucose, 3+ acetone and 1+ albumin.

Hospital Course

The left foot was treated surgically, followed by a course of penicillin. The patient was diagnosed as having diabetes mellitus and was started on regular insulin 30 units increasing up to 55 units on the third hospital day. She was switched to 40 units of insulin and later to Tolbutamide 500 mg. q. 6 h. She was discharged on September 22, 1964, on Tolbutamide 500 mg. b.i.d. and 1,200-calorie diet.

Follow-Up

The patient has been admitted to Hennepin County General Hospital on two subsequent occasions, the last on May, 1967. At that time she was found to have bitaleral retinopathy with exudates and microaneurysm scattered over both fundi. Fasting blood sugar ranged from 156 to 296; serum cholesterol 350. An electrocardiogram was read as borderline, with some ST depression in V_6. The patient was switched to Tolinase 250 mg. q. i. d. and 1,800-calorie diet. She is presently being followed at the Diabetic Clinic in the Out-Patient Department. Her latest laboratory work, July 28, 1967, showed fasting blood sugar 188, serum cholesterol 350, serum triglyceride 214 mg. %, and total blood lipids 923 mg. %.

References may be secured from the Grand Rounds Editor.

To the Young Practitioner

Your patient has no more right to all the truth you know than he has to all the medicine in your saddle-bags, if you carry that kind of cartridge-box for the ammunition that slays disease. . . . Some shrewd old doctors have a few phrases always on hand for patients that will insist on knowing the pathology of their complaints without the slightest capacity of understanding the scientific explanation. I have known the term "spinal irritation" serve well on such occasions, but I think nothing on the whole has covered so much ground, and meant so little, and given such profound satisfaction to all parties, as the magnificent phrase "congestion of the portal system."*

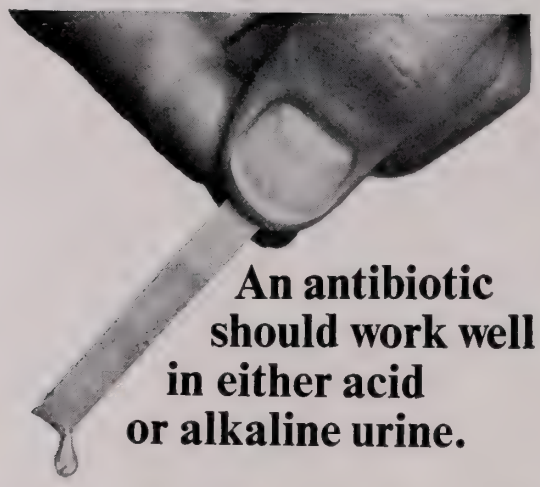
*Oliver Wendell Holmes

They May Have A Point

One of the factors encouraging quackery is the doctor's neglect of the complexity of the patient's first complaint.—J. A. Weijel

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Temperance and labor are the two true physicians of man.—Jean Jacques Rousseau



An antibiotic should work well in either acid or alkaline urine.

It isn't always necessary to adjust urinary pH in treating G.U. infections.

Not when the causative organism is a strain sensitive to DECLOMYCIN® Demethylchlortetracycline, as is often the case.

DECLOMYCIN remains stable and active in either acid or alkaline urine. So there's no need to acidify the urine to keep the antibiotic at work.

Why match the urine to the antibiotic...when you can match the antibiotic to the urine...by prescribing DECLOMYCIN. A b.i.d. dosage makes therapy convenient for your patient.

Effectiveness: DECLOMYCIN Demethylchlortetracycline should be equally or more effective therapeutically than other tetracyclines in infections caused by organisms sensitive to the tetracyclines.

Contraindication: History of hypersensitivity to demethylchlortetracycline.

Warning: In renal impairment, usual doses may lead to excessive accumulation and liver toxicity. Under such conditions, lower than usual doses are indicated, and, if therapy is prolonged, serum level determinations may be advisable. A photodynamic reaction to natural or artificial sunlight has been observed. Small amounts of drug and short exposure may produce an exaggerated sunburn reaction which may range from erythema to severe skin manifestations. In a smaller proportion, photoallergic reactions have been reported. Patients should avoid direct exposure to sunlight and discontinue drug at the first evidence of skin discomfort. Necessary subsequent courses of treatment with tetracyclines should be carefully observed.

Precautions: Overgrowth of nonsusceptible organisms may occur. Constant observation is essential. If new infections appear, appropriate measures should be taken. In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment.

Side Effects: Gastrointestinal system – anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin – maculopapular and erythematous rashes; a rare case of exfoliative dermatitis has been reported. Photosensitivity; onycholysis and discoloration of the nails (rare). Kidney – rise in BUN, apparently dose-related. Transient increase in urinary output, sometimes accompanied by thirst (rare). Hypersensitivity reactions–urticaria, angioneurotic edema, anaphylaxis. Teeth – dental staining (yellow-brown) in children of mothers given this drug during the latter half of pregnancy, and in children given the drug during the neonatal period, infancy and early childhood. Enamel hypoplasia has been seen in a few children. If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy. Demethylchlortetracycline may form a stable calcium complex in any bone-forming tissue with no serious harmful effects reported thus far in humans.

Average Adult Daily Dosage: 150 mg q.i.d. or 300 mg b.i.d. Should be given 1 hour before or 2 hours after meals, since absorption is impaired by the concomitant administration of high calcium content drugs, foods and some dairy products. Treatment of streptococcal infections should continue for 10 days, even though symptoms have subsided.

Capsules: 150 mg; Tablets: film coated – 300 mg, 150 mg and 75 mg of demethylchlortetracycline HCl.

355-B

DECLOMYCIN®
DEMETHYLCHLORTETRACYCLINE

Lederle LEDERLE LABORATORIES, A Division of American Cyanamid Company, Pearl River, New York



Abstracts, Briefs and Commentaries

METASTASES FROM SQUAMOUS CELL CARCINOMAS OF THE SKIN

The authors with the assistance of the California Tumor Registry studied 6,900 squamous cell skin cancers for metastatic potential. Out of the total number of cases studied there were 142 cases with metastases to the regional lymph nodes or distant sites. This represented 2% of the total number of cases studied. In their study the authors did not include squamous cell cancer of the mucous membranes. Out of the total number of patients studied, the median age was 72 years with women having a median of 77 years, while the median age for men was 69. In their series 67% of the primary lesions occurred on the exposed areas of the body. The authors point out the importance of malignant degeneration ensuing from actinic change in the skin and the metastatic potential of such lesions. Of the 142 squamous cell skin cancers which were reported to have metastasized (2% of the 6,900 cases studied), metastases reached the lung in approximately 4.9%; and in 6% spread was considered to be generalized. Of the group of 117 patients who were followed for at least five years after diagnosis, 57% died of their skin cancer.

Comment: The authors point out that some studies in recent years have led to a complacency concerning the metastatic potential of squamous cell carcinoma of the skin. This report shows that squamous cell carcinomas of the skin which arise from actinic change as well as those which arise from chronic ulcers and radiodermatitis may and do metastasize. Even though squamous cell carcinomas of the skin are considered to be of low malignant potential, they are nevertheless capable of widespread metastatic disease. Therefore they should be diagnosed early and treated aggressively, with an adequate follow-up of at least five to 10 years.

Willard C. Peterson, Jr., M.D.
Minneapolis, Minnesota

Epstein, E., Epstein, N.N., Bragg, K., Linden, G., Arch. Derm. 97:245, 1968.

THE PILL AND PSEUDOCANCER OF CERVIX AND BREAST

In the January 29 issue of JAMA, Candy and Akell, of the pathology department at the University of Michigan, reported 12 patients with adenomatous hyperplasia of the cervix. Most cervixes had malignant looking verrucose or polypoid masses at the squamous columnar junction. Eight patients had taken Enovid, three Ortho-Novum, and one Provera. In two thirds of patients, clinicians considered the lesions malignant. Further, pathologists interpreted three biopsies as adenocarcinoma, and patients were sent to University of Michigan for radiation. These pathologists recognized all 12 cervical growths as adenomatous and cribiform hyperplasia of gland and reserve cells. No lesions recurred after they were excised or cauterized.

About one week after the JAMA article, a report appeared in the January issue of the *American Journal of Clinical Pathology* on Enovid-induced breast masses. Its authors, three pathologists at the University of Washington, report four patients, aged 35, 31, 20, and 21, who had "florid" fibroadenomas. These patients had taken Enovid from two months to two years, and they presented with firm breast masses. In each case, surgeons easily enucleated the nodules, but the masses' hardness concerned them. The pathologists, in their turn, were disturbed by the "severe epithelial proliferation." Finally the presence of secretory droplets in cells, lack of cellular atypism, and the existence of capsule convinced them the lesions were benign. When the patients were followed for 10 to 44 months, no lesions recurred. The authors did, however, see three more breast biopsies with Enovid-induced fibroadenomas.

Richard L. Reece, M.D.
Minneapolis, Minnesota

References

1. Candy, M. and Akell, M.: Progestogen. Induced Adenomaton Hyperplasia of Uterine Cervix. JAMA 203:323, 1967.
2. Goldenberg, V. E., Wiegenston, L., and Mottet, Nik.: Florid Breast Fibroadenonas in Patients Taking Hormonal Oral Contraceptives. *American Journal Clinical Pathology* 49:52, 1968.

MALIGNANT TUMORS IN SMALLPOX VACCINATION SCARS

Malignant degeneration occurring in a prior vaccination scar is a delayed complication to this procedure which has recently received increased attention. In the present study the authors report on 24 patients with proven malignant tumors originating in smallpox vaccination scars. The tumors included malignant melanoma, squamous cell carcinoma and basal cell epithelioma. The period of latency between the vaccination and occurrence of the tumor was in most cases many years. The authors, because of this prolonged latent period, concluded that a viral etiology for the occurrence of tumors in vaccination scars was only a remote possibility. A more plausible suggestion was the tendency of older scars to undergo malignant degeneration. Another factor to consider was the individual susceptibility of each of the patients studied to develop cutaneous cancer (six of 13 patients who developed basal cell carcinomas in their vaccination scars had multiple tumors). It is concluded that further clinical, epidemiological, and laboratory studies should be made to determine if the vaccinia virus has any role in the production of malignant tumors in man.

Willard C. Peterson, Jr., M.D.
Minneapolis, Minnesota

Marmelzat, W. L.: Arch Derm 97:400, 1968.

GALLBLADDER DISEASE IN DIABETICS

Diabetics do not withstand the complications of gallbladder disease as well as other people.

Between 1947 and 1960 a total of 145 diabetics with cholelithiasis and cholecystitis were admitted to Massachusetts General Hospital. Mundth compares results in these cases with those in 150 nondiabetics operated on for acute cholecystitis.

Of the 145 diabetics 43 were treated without operation. Of the 102 patients treated surgically, 99 had a cholecystectomy with or without exploration of the common duct, and three had a cholecystostomy.

The operative mortality was 22 percent and the incidence of postoperative complications was 51 percent in the surgically treated diabetics, as compared with 0.7 percent and 11 percent respectively in the nondiabetics. Diabetics have a special liability to gallstones; incidence is 25 percent in diabetics against 8 percent in nondiabetics.

Patients with mild diabetes tolerated elective biliary tract surgery very well. The operative mortality and morbidity were not significantly different from those in nondiabetics.

It is recommended that early elective cholecystectomy should be carried out in all diabetics known to have cholelithiasis, unless a specific contraindication is present.

Courtesy of World-Wide Abstracts

Mundth, E.: New Eng J Med 267:13:642.

PHOTOSENSITIVITY STUDIES WITH DEMETHYLCHLORTETRACYCLINE AND DOXYCYCLINE

In this study 30 health volunteers were used as subjects. Ten of the volunteers were given demethylchlortetracycline (600 mg a day), 10 were given doxycycline (200 mg a day) and 10 were given a placebo. The volunteers were on their respective medication for one week, and then exposed to five hours of sunshine off the southeast coast of Florida. Following this exposure the subjects were examined by three physicians who were unaware which drug each person had been taking. Results were as follows: nine out of 10 subjects taking demethylchlortetracycline showed what was interpreted as a photosensitive type of eruption; two of the ten receiving doxycycline had similar reactions. One person on the placebo showed an exaggerated response.

Comment: The authors point out that sun-induced reactions to demethylchlortetracycline are believed to be phototoxic in nature and that there is a high degree of susceptibility to this reaction among most people who receive the drug if adequate sun exposure follows. They also concluded that on the basis of the information in the present study, the use of doxycycline would be associated with less photosensitivity than demethylchlortetracycline.

Willard C. Peterson, Jr., M.D.
Minneapolis, Minnesota

Blank, H., Cullen, S.I., Catalano, P.M.: Arch Derm 97:1, 1968.

PERSISTENT CARCINOMA OF CERVIX

A pathological review of 83 pelvic exenteration specimens for persistent or extensive carcinoma of the cervix showed the carcinoma to be more extensive than clinically apparent. The urinary bladder was invaded in 61% of the cases and the rectosigmoid in 44%. A poor prognosis was associated with large bowel invasion, but 27.7% of the patients survived for five years. Sur-

vival was mostly dependent on finding lymph node metastases. The most characteristic alteration of irradiation was the finding of subintimal foam cell plaques in small arteries, especially near the sites of necrosis.

Courtesy of References and Reviews
Journal of the American Medical Association

Perez-Mesa, C., and Spjut, H.: Arch Path 75:462, 1963.

PERITONEAL DIALYSIS IN SALICYLATE POISONING

Four cases of salicylate intoxication were treated by continuous peritoneal dialysis. Observations showing the extensive depletion of available body base, especially potassium, are reported. The clinical states appear to parallel these, rather than the serum salicylate levels. During dialysis the major repair process is correction of electrolyte depletions, which permits the effective renal excretion of salicylate. The various therapeutic measures available for treating salicylate intoxication are reviewed. Peritoneal dialysis is the simplest and most freely available of these. It is suggested on the basis of this experience that prevention of salicylate intoxication now depends largely on accuracy of information in manufacturers' advertising.

Courtesy of References and Reviews
Journal of the American Medical Association

Elliot, G., Crichton, J., and Miller, G.: Anesth Analg 42:338, 1963.

The Content of Milk*

Content	*Cow*	*Sheep*	*Camel*	*Human Mother's*	*Donkey*	*Goat*
Protein	4%	6.52	3.45	0.8– 1.5	1.98	3.5
Fat	4.1	6.86	3.02	3.0– 4.0	1.45	5.0
Galactose	4.8	4.91	5.15		6.24	2.5
Water	87	80.82	87.67	87 –88	89.88	88.7
Ash	.72	.89	.71		.45	.7

*See Page 1354.

Modern Confucius

The superior man understands what is right; the inferior man understands what will sell.

The superior man loves his soul; the inferior man loves his property.

The superior man always remembers how he was punished for his mistakes; the inferior man always remembers what presents he got.

The superior man blames himself; the inferior man blames others.

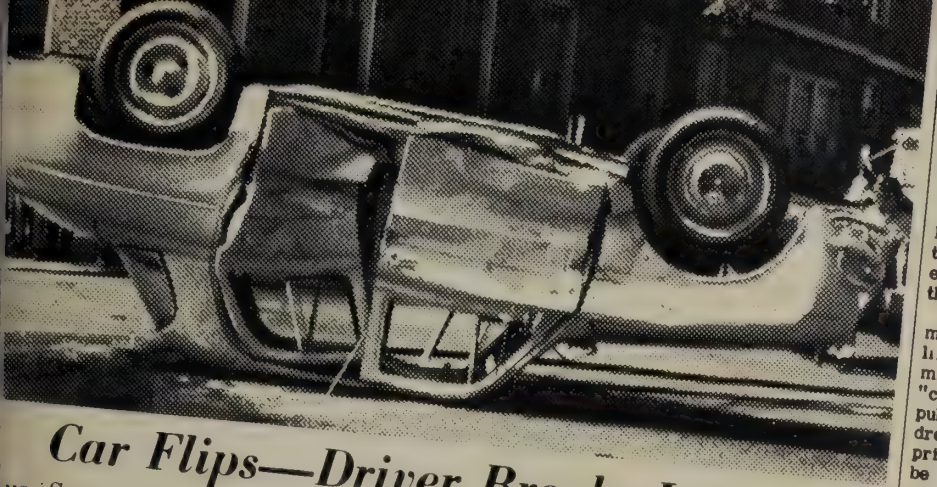
The superior man is always candid and at ease with himself or others; the inferior man is always worried about something.

A man who has committed a mistake and doesn't correct it is committing another mistake.

Patient's Dilemma

The doc says I'm sound as a dollar-
And I know he's wise in his ways,
But this is the thing that disturbs me,
How sound is a dollar these days?

—Uncle Mat in Bagology



STAFF PHOTO

Car Flips—Driver Breaks Leg

...us, Sept. 7. John P. Jones of ... incurred a broken leg today ... driving ... Patrolman B. R. Brown, the car hit a fire hydrant and flipped over on its ... Hasn't he ... car.

issue, a... tember t... fications' ... ton dicta... Althou... made Mo... down by a ... ter shar... flat obje... was pass... Board ... McCredi... tion" s... elimir... the st... The c... ment ca... limit ra... mile li... "cut-of... public ... dren ... priv... be b... or th... schoo... The ... so so... rathe... burs...

He's had enough excitement for one day.

For the patient who has been through an accident, the worry and anxiety following the experience may actually heighten the perception of pain. This is why there's a classic 1/4 grain *sedative* dose of phenobarbital in Phenaphen with Codeine—*to take the nervous "edge" off,* so the rest of the formula can control the pain more effectively.

Phenaphen® with Codeine

Phenaphen® with Codeine No. 2, No. 3, or No. 4 contains: *Phenobarbital* (1/4 gr.), 16.2 mg. (Warning: may be habit forming); Aspirin (2 1/2 gr.), 162.0 mg.; Phenacetin (3 gr.), 194.0 mg.; Hyoscyamine sulfate, 0.031 mg.; Codeine Phosphate, 1/4 gr. (No. 2), 1/2 gr. (No. 3), or 1 gr. (No. 4). (Warning: may be habit forming).

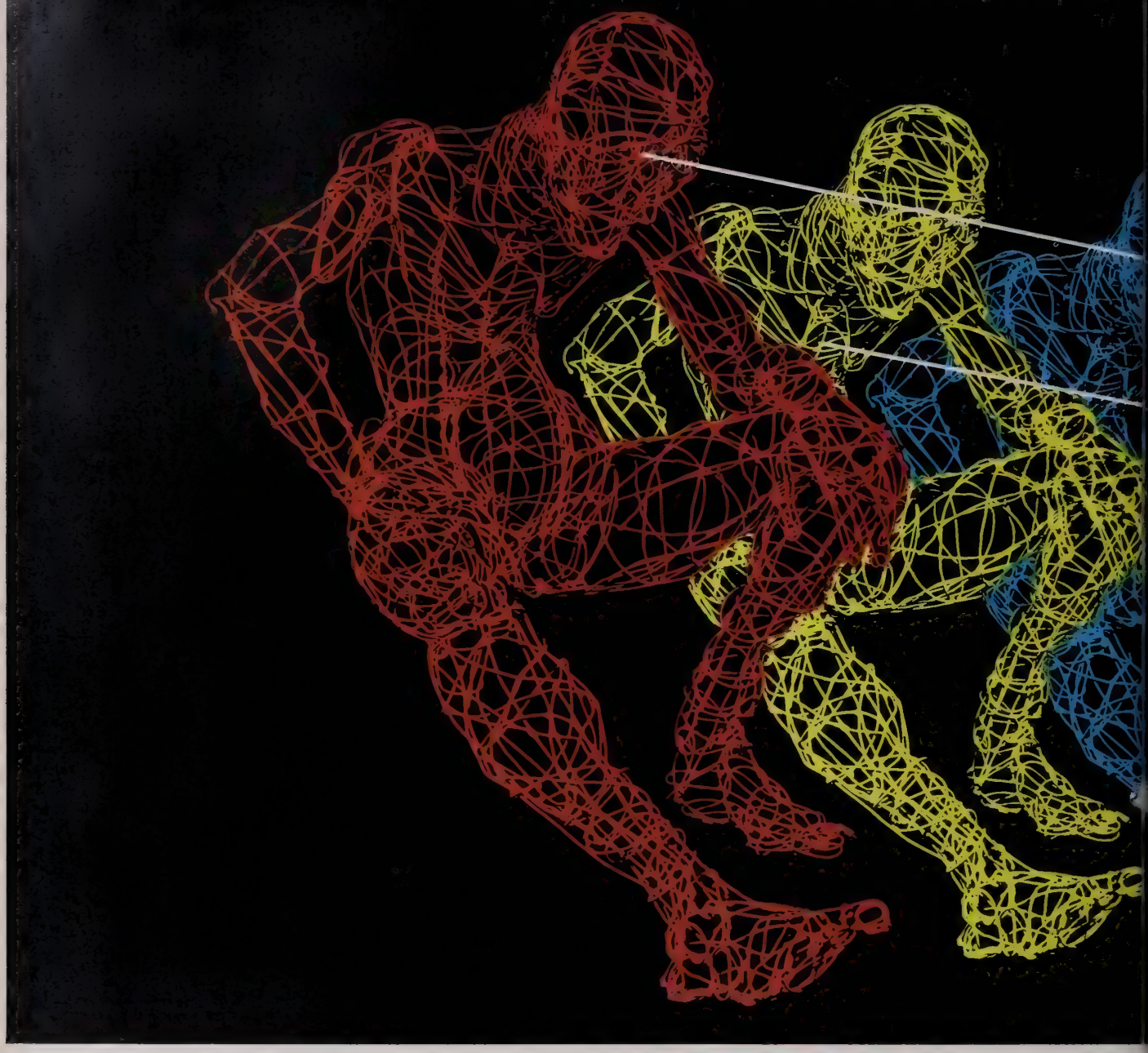
THE COMPOUND ANALGESIC THAT CALMS INSTEAD OF CAFFEINATES

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Cobalamin Concentrate, N.F., equivalent to Cobalamin (The total vitamin B_{12} activity in the Special Liver-Stomach Concentrate, Lilly, and the Cobalamin Concentrate, N.F., is 15 micrograms.)	7.5	mcg.
Iron, Elemental (as Ferrous Fumarate)	110	mg.
Ascorbic Acid (Vitamin C)	75	mg.
Folic Acid	1	mg.

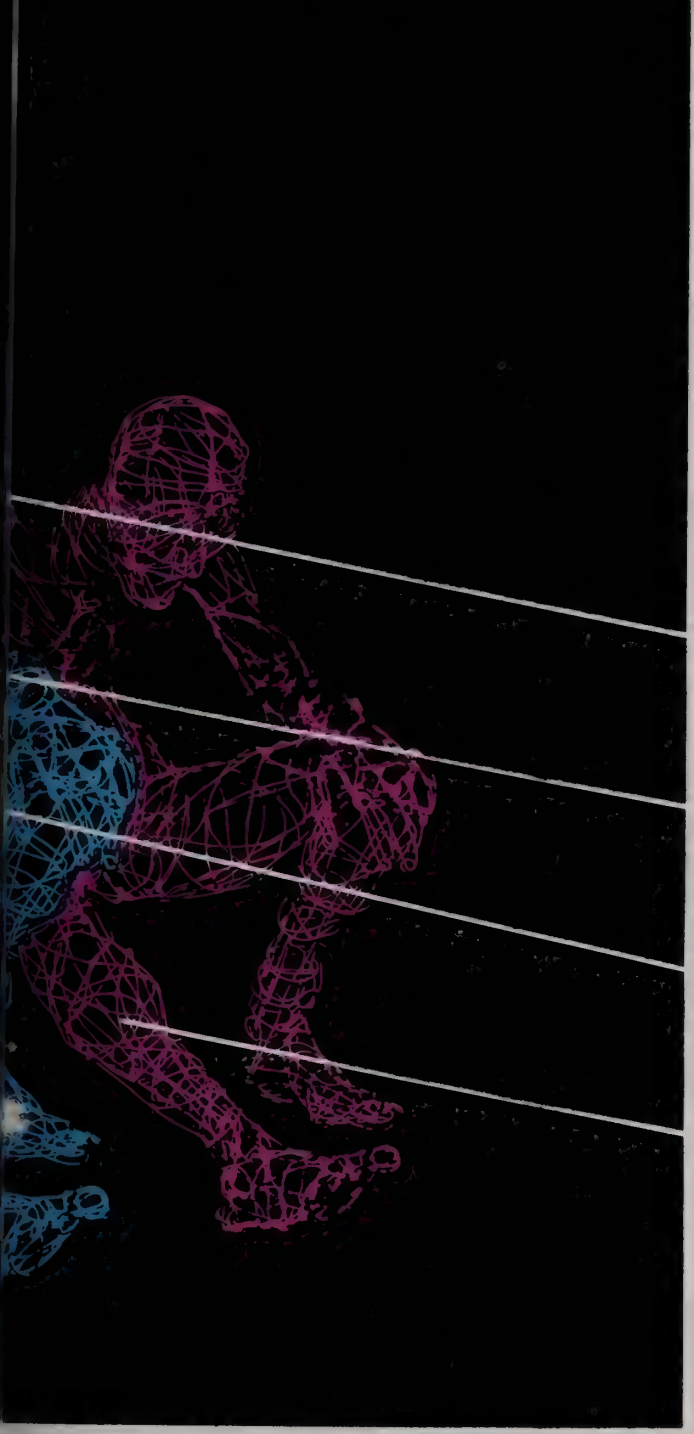
Indications: Trinsicon® (hematinic concentrate with intrinsic factor, Lilly) is a multifactor preparation effective in the treatment of anemias that respond to oral hematinics, including pernicious anemia and other megaloblastic anemias and also iron-deficiency anemia.

Contraindications: Hemochromatosis and hemosiderosis.

Precautions: Anemia is a manifestation that requires appropria investigation to determine its cause or causes.

In pernicious anemia, the use of folic acid without adequa vitamin B_{12} therapy may result in hematologic remission but ne rological progression. Adequate doses of vitamin B_{12} (parenter or oral with potent intrinsic factor as in Trinsicon® [hematir concentrate with intrinsic factor, Lilly]) usually prevent, halt, improve the neurological changes.

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The Physician's Workshop

In Spring a Young Man's Fancy Turns to - -

IN THESE EXCITING times of great surgical advances, medical men cannot help but be stimulated to strive harder to solve tough medical problems.

The following account of a lay attempt to transplant a bean into a human being may be of interest: immediate voluntary rejection by the host created a challenging problem for his medical attendant.

A mini-corkscrew and a mini-orifice (the external auditory meatus) were featured in this spring-time happening. The 17-year-old patient was planting beans known to some as black-eyed peas. This bean is kidney-shaped and has a thin, very friable skin. The interior is composed of dry, hard starch stored to provide the sprouting plant with food. The bean measures 10 mm in length, 20 mm in girth and about 7 mm in diameter in the midsection.

For some reason the patient decided to plant one experimentally in his left ear and it progressed down the auditory canal to be stopped by the tympanum. The consequences of his action gradually dawned upon him as attempts to remove this seemingly innocuous object failed. Naturally he sought medical help, and, of course, it was on a weekend.

He was fortunate in finding a doctor sympathetic and willing to wrestle with his problem. The doctor found the bean tightly wedged, a perfect fit, deep in the osseous portion of the auditory canal so that removal by retrograde water-jet was impossible. The end of the bean could just be discerned in the canal and any pressure applied to the bean was transmitted to the tympanum and evoked immediate distress. An attempt was made to grasp the bean by means of mosquito hemostats in the hope that the skin would be strong enough to permit the whole bean to be withdrawn intact. Needless to say, the skin broke at once. Further attempts at grasping the bean resulted in crumbling of the visible portion until it became obvious that removal was going to require the skills of a specialist. It was feared that possible delay with consequent swelling of the bean by absorption of moisture would be detrimental—quite apart from the possibility of the bean sprouting out of his ear.

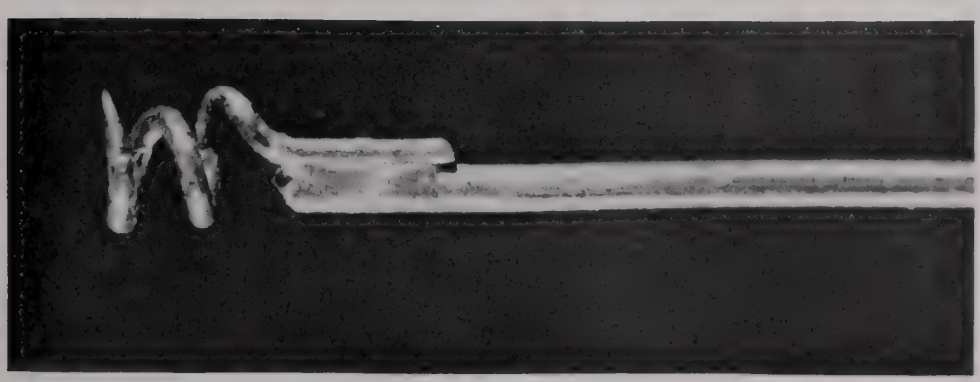


Figure 1

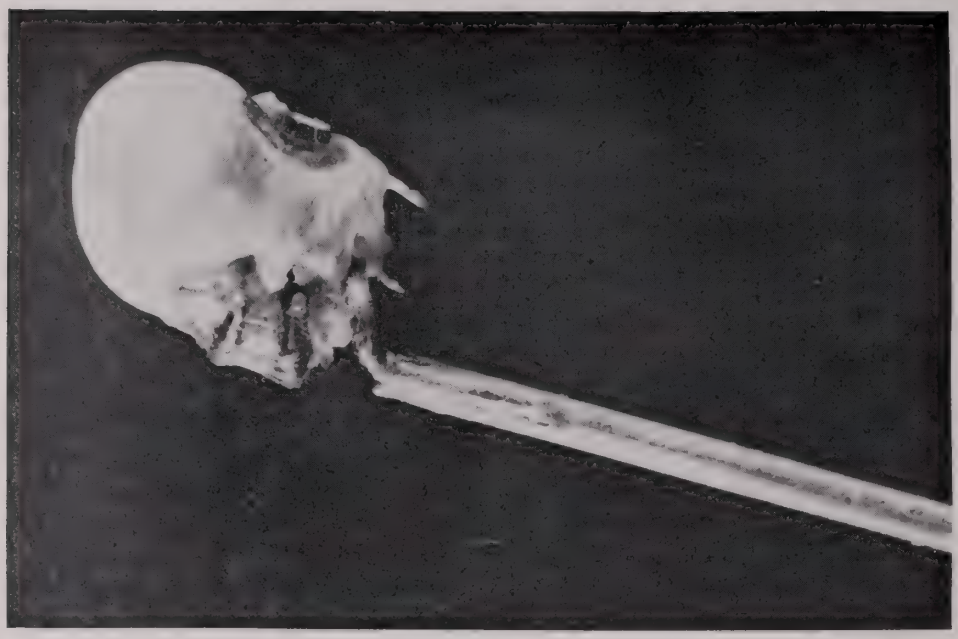


Figure 2

The young patient was a man of moderate means and limited patience; so the problem required the utmost ingenuity to solve quickly and economically. Hooking was tried by bending a sharp pin point, but it was found impossible to slide the hook down between the bean and the lining membrane of the canal because of the exquisite sensitivity of the membrane.

A mini-corkscrew was the answer to the problem of removal. A sharp pointed steel sewing pin was coiled around a small nail held in a vise, taking care not to damage the point. The head of the pin was cut off and the shaft was soft soldered to a piece of stiff brass wire. The finished instrument is shown in Figure 1. The corkscrew coil measured 3 mm in outside diameter. The point was carefully bent so as to lie within the major diameter of the coils of the corkscrew in order to avoid trauma to the lining membrane of the auditory canal as the instrument was rotated.

The finished instrument was carefully screwed into the bean and it was surprising how much force was necessary to extract the bean shown attached to the corkscrew in Figure 2. Happily the patient was able to return to his bucolic pursuits at once and has had no sequelae.

The author will be most happy to donate this instrument to or to make one for any of his colleagues who may anticipate such a problem in their practice.

J. J. Wild, M.D.
Minneapolis, Minnesota

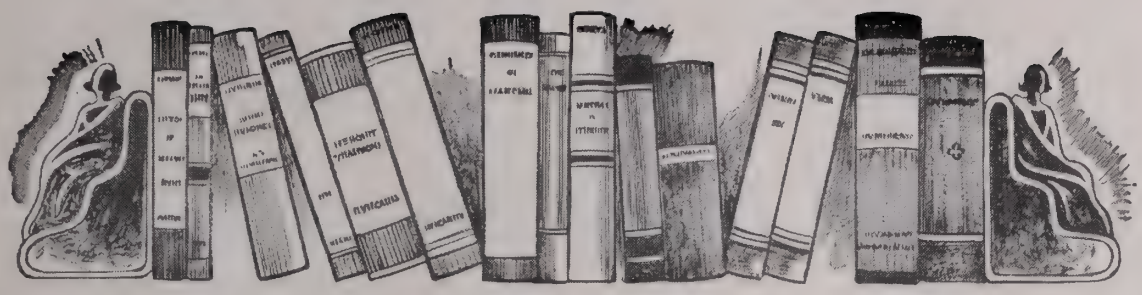
By working faithfully eight hours a day, you may eventually get to be a boss and work twelve hours a day.—Robert Frost

---

There are two kinds of men who never amount to much: those who cannot do what they are told, and those who can do nothing else.—Cyrus Curtis

---

Drawing on my fine command of language, I said nothing.—Robert Benchley



Book Reviews

A book is a mirror: if an ass peers into it, you can't expect an apostle to look out.—Georg Lichtenberg

TEXTBOOK OF ANATOMY AND PHYSIOLOGY IN RADIOLOGIC TECHNOLOGY—By Charles A. Jacobi. 421 pages. 187 illustrations. Published by C. V. Mosby, 1968. Price $12.00.

This 200-page monograph fulfills the necessity of providing a good practical working knowledge of anatomy and related physiology for students of radiologic technology. The material presented in this text has a readable style and a simple organizational structure. Each chapter is annotated with an adequate bibliography and reference source. The illustrations are plentiful and are excellently reproduced.

There are 12 chapters in this text. Chapters 1, 2, and 3 introduce the reader to anatomy and physiology, body structures and functions, and an embryologic survey. The remaining chapters expose the nine commonly recognized body systems.

Perhaps the greatest compliment that can be given this text is the space in which the material is presented. Mr. Jacobi does not overstress any particular subject, but covers quite adequately all the important needed information for the radiologic technology student. I highly recommend this book for all schools of Radiologic Technology.

Philip J. Griswa, R.T., B.S.*
Minneapolis, Minnesota

*Chief Radiologic Technologist and Director, School of X-ray Technology, Hennepin County General Hospital.

THE CARE OF THE GERIATRIC PATIENT—E. V. Cowdry, 430 pp., C. V. Mosby, St. Louis, 1968, $15.75

This is the third edition of Cowdry's editorship of a book on this subject. Cowdry compares geriatrics to pediatrics and considers that the science of the aged is as deserving of special attention by the profession as infant care. Just as a five-year-old is not just a small man, so a seventy-year-old is not just a shriveled adult. Chapters on nursing care, nursing homes, home care, living arrangements, and rehabilitation point out how many ancillary needs of the aged must be considered along with total medical care. There is also a chapter on spiritual aspects written by a Catholic, a Protestant, and a Jew concerning the needs of the members of these faiths. The value of clerical help in a hospital would be enhanced if any of the three would address himself also to the spiritual problems of the patients uncommitted to these religions, or perhaps to any.

Reuben Berman, M.D.
Minneapolis, Minnesota

PRACTICAL AUTOMATION FOR THE CLINICAL LABORATORY—By Wilma L. White, Marilyn M. Erickson, and Sue C. Stevens, C. V. Mosby Co., St. Louis, 1968, 401 pages, $14.50.

What makes American technology go? Brainpower? Our educational system? Our organizational and managerial talents? Wealth? Resources? Or is it the computer? Take your pick, and you will be partly right. But only partly! According to Eric Hoffer, sage of San Francisco's waterfront, our skill at maintaining equipment forms the bedrock that supports our technocratic suprastructure.

We suspect he is right. After all, in this land teenage boys think little of taking apart and rebuilding car engines, many citizens successfully repair household appliances, and an army of men keep the wires open, eviscerate the innards of computers, and are at home with circuits, gears, fuses, switches, vacuum tubes, and transistors.

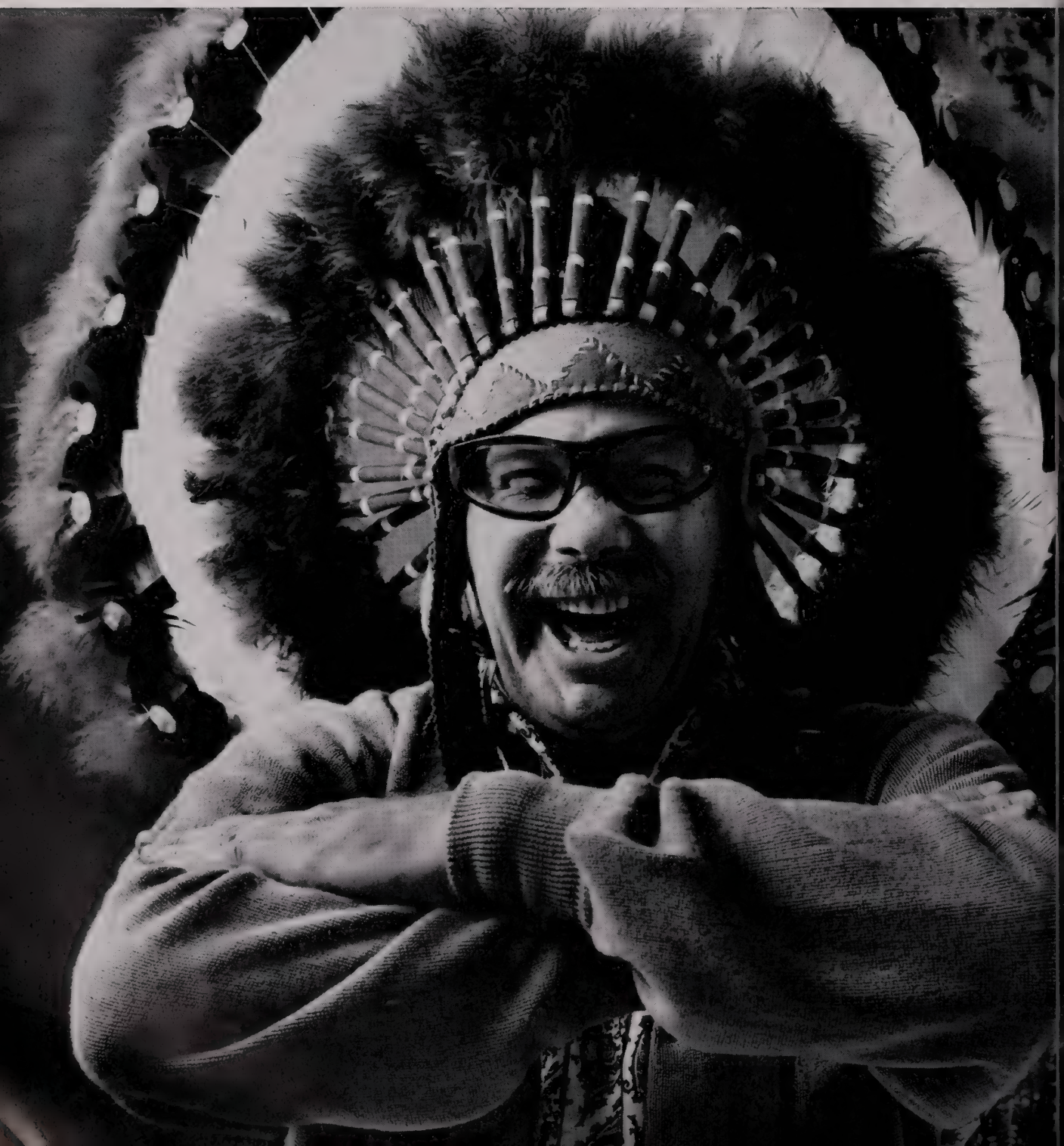
Yet in hospital laboratories, much automated equipment takes weeks to crank up, breaks down, or lies idle for want of maintenance. Why? Lack of a mechanical bent on the part of technologists and pathologists? Too much to do and too little time to do it? Fragile instruments pushed onto the market too soon? Neglect? Or is it because laboratory people fail to anticipate, to prevent, and to detect problems?

All, to a greater or lesser extent, contribute. But another headache is lack of a maintenance manual written by those who nurse their automated instruments through times of toil and trouble. This book should provide some relief.

Technologists and pathologists will gain practical information by dipping into the pages of this text, but physicians seeking a source book to help them interpret results for diagnosis or to digest data will find little to aid them. We recommend the book for its intended audience.

Richard C. Reece, M.D.
Minneapolis, Minnesota

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Special Article

Community Measles Clinics and the Physician

D. S. FLEMING, M.D.*
Minneapolis, Minnesota

A NATION-WIDE flood of measles vaccination campaign materials—including even Peanuts cartoon strips—issuing from the U.S. Public Health Service in the past few years cannot have escaped concern from members of the medical profession. Physicians are justifiably wary of such crash programs, especially in view of the near tragedies stemming from such recent events as the jaundice traced to yellow fever vaccine during World War II and the vaccine-related poliomyelitis cases of the "Cutter Incident." Nevertheless, the national measles eradication program has earned the support of nearly every concerned professional organization.

The fulfillment of school entry requirements for measles immunization should not, however, obscure the larger objectives of the measles eradication program of virtual elimination of all susceptibles in all age groups. County-wide public measles clinics have been conducted in over 50% of Minnesota's counties with a resulting large increase in vaccine utilization in both private physicians' offices and public clinics.

Background

Measles has been reportable in Minnesota since 1910 and Department of Health records show that reported incidence has ranged from an all-time high of 29,759 cases in 1935 to a low of 140 cases in 1967. Measles deaths have ranged from a high of 282 in 1923 to no deaths in 1964 and 1967. The average annual number of cases from 1954 through 1963 was 3,401; the average number of deaths was six.

Live attenuated measles virus vaccine was licensed in the U.S. in 1963 and was added to the Federal Vaccination Assistance Grant. Local projects in Minneapolis, St. Paul, and Rochester-Olmsted County began distributing the vaccine from federal sources in July, 1966. The state project began July 1, 1967, incorporating the dual objectives of (1) stimulation of measles immunization with vaccine pur-

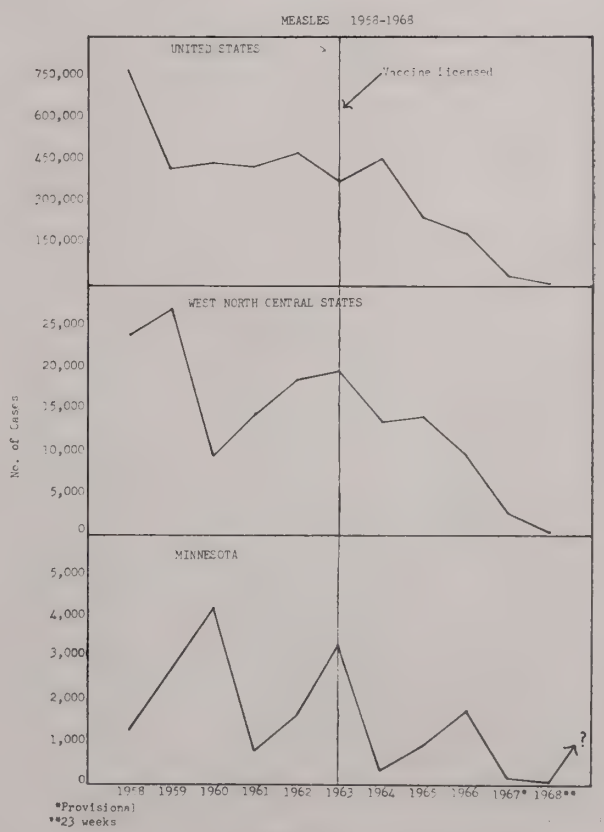


Figure 1

*Director, Division of Disease Prevention and Control, Minnesota Department of Health.

chased by both federal and state funds, and (2) the development of a newborn follow-up "maintenance" program to inform parents of the need for all the common immunizations at the appropriate age.

The Downward Trend

Figure 1 shows the reported measles cases in the U.S., the west-north central states, and Minnesota since 1958.[1] From this data two inferences may be drawn. First, the decline of measles in Minnesota reflects both the use of vaccine by Minnesota's physicians in the years 1963-66 and the general trend throughout the country. Second, an increase in the occurrence of measles in 1969 may be expected if the trend in Minnesota since 1963 continues.

Public Clinics in Minnesota

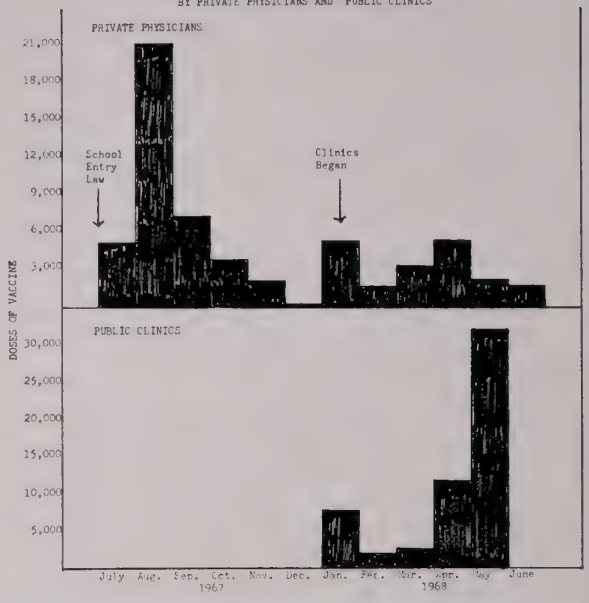
Many areas had already held measles clinics in the past few years, but additional scope and efficiency of these clinics became possible with the new capacity of the Department of Health to provide the working "tools," for example, the jet guns for economical and efficient injection of vaccine from multiple dose vials at rates of 600-800 doses per hour (Figure 2).

From January to May, 1968, 47 of Minnesota's 87 counties (Figure 3) conducted measles immunization clinics, nearly all with the use of the jet gun; a total of over 60,000 doses of vaccine were distributed in this way.

Table 1 shows the monthwise distribution of vaccine by clinics and by private physicians. It

TABLE 1

MONTH-WISE DISTRIBUTION OF MEASLES VACCINE BY PRIVATE PHYSICIANS AND PUBLIC CLINICS



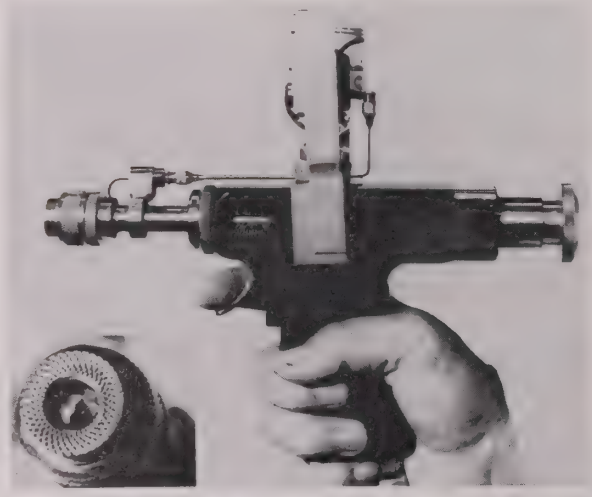




Figure 2

can be seen that a remarkable rise in vaccine utilization by private physicians occurred in response to the school entry legislation in the summer of 1967. This effect of mass clinics has been noted throughout the U.S.: that is, the balance between immunizations given privately and publicly does not change when a community promotes immunization with mass clinics.[3] Both groups experience an increased demand for services with a resulting improvement in community protection. Furthermore, the turnout for mass clinics has been shown to be greater when a small donation (25-50c) is asked than when the vaccination is "free," additional evidence that free services are not valued highly.

Theoretical Considerations

Every disease can be defined as distinctly by its epidemiologic characteristics as by its clinical or pathologic features. Because the epidemiology of measles is unique, unwarranted parallels between it and other common illnesses, for which effective vaccines have been used, may be misleading. In this regard, the possible danger of a susceptible adult population is

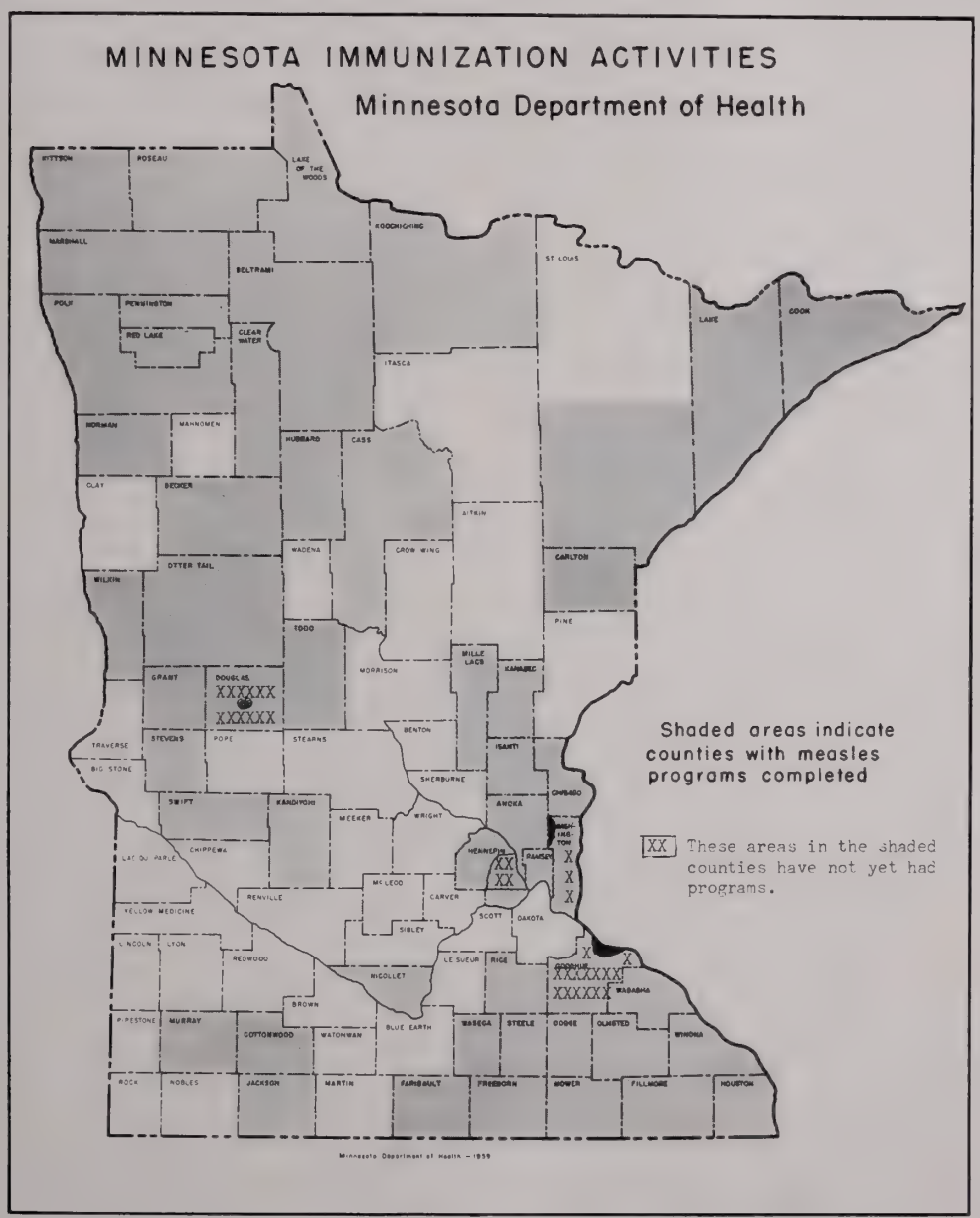


Figure 3

foremost.

The Immune Populace

Table 2 illustrates that the natural occurrence of measles results in the immunity of over 90% of a susceptible population by age 15 years. With widespread use of an effective vaccine and the subsequent dramatic decline in the occurrence of measles cases, the ultimate proportion of measles-immune adults will gradually fall, reflecting only the use of the vaccine. Vaccination of 60-75% of the population may be effective in preventing major outbreaks and therefore also in preventing the exposure of other unvaccinated susceptibles in childhood.

The Susceptible Population

A measles vaccination law may therefore provide a needed safeguard to prevent the repetition of the Faroe Island experience in which 50% of a susceptible population died during a measles epidemic.[4] More than one approach may be necessary, however, to reach all the objectives of the vaccination plan.

The shortcomings of a single approach have been suggested by a 1967 study in Hopkins County, Kentucky, with an experimental and a control group of infants demonstrating that letters sent to parents urging measles immunization through private physicians had no discernible effect on increasing the number immunized in the experimental over that in the control group.[5] At best, only about one half of the children one to two years of age were protected. Data of this nature is subject to the limitations of socioeconomic variables, but it is not encouraging.

Comments and Conclusions

The national commitment to measles eradication, however controversial as a priority or possibility, is an accomplished fact with implications for every state. On the one hand are the natural reactions of many physicians and taxpayers such as:

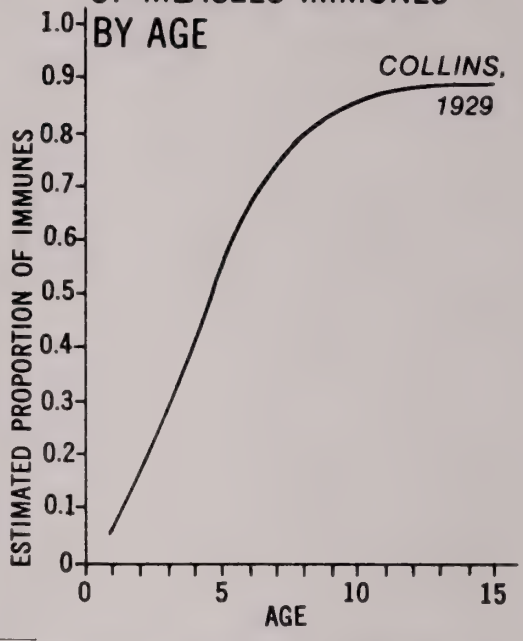
"Immunizations are the responsibility of the individual family and physician."

"Measles immunizations have been adequately done through private physicians' offices in this state."

"This is another government 'dole' ".

TABLE 2*

ESTIMATED PROPORTION OF MEASLES IMMUNES BY AGE



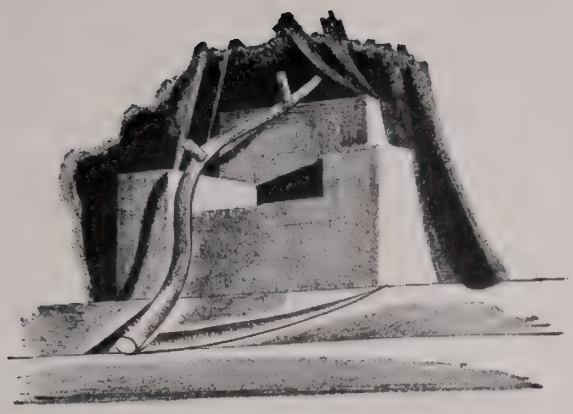
*Measles Eradication—1967, U. S. Public Health Service.

On the other hand is the reality of governmental assistance in money, supplies, and personnel to help achieve higher levels of immunization against many diseases. Fortunately Minnesota is achieving the objectives of both groups with mutual understanding and objectivity, and with practical benefits to all.

A Federal Vaccination Assistance Grant* has made possible the purchase of measles vaccine for every Minnesota child from age one to 12 years. Over 70,000 doses of this vaccine have been distributed in the first five months of 1968 through public clinics and private physicians' offices. Although compliance with the measles school entry requirement should eventually insure the vaccination of a large percent of the population, a current "one-time-only" approach through public clinics should be completed in 1968 if a resurgence of measles in 1969 is to be prevented and if we are to insure that a significant number of older children now in school but unaffected by the school entry law will not reach their adult years susceptible to the hazards of adult measles.

*$204,603 with $95,290 of matching state funds.

References may be secured from the author or the reprints.



In Memoriam

All human things are subject to decay, And when fate summons, monarchs must obey.—DRYDEN

OSCAR B. BERGMAN, M.D.

Dr. O. B. Bergman, St. James physician for 40 years, died June 25. Born in Sweden, Dr. Bergman came to the United States at the age of one. He attended schools in Foley and St. Cloud and graduated from the University of Minnesota Medical School in 1924. After practicing in Janesville for two years, he went to St. James where he had since practiced.

Dr. Bergman was a member of the St. James school board for 18 years, the Lions Club, American Legion, American Medical Association, Blue Earth Valley Medical Society and a Life Member of the Minnesota State Medical Association.

He is survived by his wife and two daughters.

THOMAS LOWRY, M.D.

Dr. Thomas Lowry, 58, a Minneapolis physician and a clinical professor of medicine at the University of Minnesota, died August 7, due to an internal hemorrhage. He was born in Minneapolis and graduated from Princeton University and the Cornell University Medical School.

Dr. Lowry began practice in Minneapolis in 1939 and at that time joined the University of Minnesota medical staff. From 1950 to 1962 he served as medical director of General Hospital. At the time of his death, Dr. Lowry was a member of the board of directors of the Hennepin County Medical Society, and a member of the Minnesota Society for Internal Medicine, the Minnesota Academy of Medicine, the Minneapolis Society of Internal Medicine, the Minnesota Society for the Study of Diseases of the Heart and Circulation, the American Medical Association and the Minnesota State Medical Association. The Minneapolis Medical Research Foundation, Inc., the reserach arm of General Hospital, was begun under his direction.

He is survived by his wife, Dr. Elizabeth Lowry, two sons and three daughters.

ARRAH B. EVARTS, M.D.

Dr. Arrah Evarts, 89, Rochester physician died April 3. She was born in Dodge Center and obtained her medical degree at the Minneapolis College of Physicians and Surgeons, Hamline University.

She retired June 1, 1936, from the staff of the Rochester State Hospital where she was senior assistant physician. She had joined the staff of the Hospital in 1918. Previous to that time she had served six years as a member of the staff of St. Elizabeth's Hospital, District of Columbia.

She was a member of the American Medical Association, and the Zumbro Valley Medical Society and a 50 Club and Associate Member of the Minnesota State Medical Association.

JAY C. DAVIS, M.D.

Dr. Jay Davis, 68, Minneapolis physician, died May 31. Born in Ogden, Iowa, Dr. Davis received his medical degree from the University of Minnesota. He was a former associate in the Department of Medicine at the Minneapolis General Hospital and a member of the faculty of the Department of Medicine at the University of Minnesota Medical School. Dr. Davis was an authority on methods for detecting bile pigments in the blood and was widely known in connection with diseases with liver and blood.

He was a member of the American Medical Association and the Hennepin County Medical Society and an Associate Member of the Minnesota State Medical Association.

He is survived by his wife.

CHARLES WILLIAM MAYO, M.D.

Dr. Charles W. Mayo, emeritus senior surgeon of the Mayo Clinic and representative of the third generation of Mayos to practice in Rochester, died July 28, of injuries sustained when his automobile left a country road in Rochester.

Born in 1898, the son of Dr. Charles Horace Mayo and Edith Graham Mayo, he was educated in a public

Charles William Mayo, M.D.
(Continued)

school in Rochester. His degree of bachelor of arts was obtained from Princeton University and that of doctor of medicine from the University of Pennsylvania. In 1927 he returned to Rochester as a fellow in surgery of the Mayo Graduate School of Medicine. He was appointed consulting surgeon and head of a section in general surgery in the Mayo Clinic in 1931, and in 1932 was appointed an instructor in surgery in the Mayo Graduate School of Medicine. Later he was advanced to assistant professor in 1935, associate professor in 1940 and professor in 1947. He became senior surgeon of the Mayo Clinic in 1960 and in 1963 retired from the Mayo Clinic.

The contributions of Dr. Charles Mayo encompassed many facets of life. He met the personal challenge of living up to a famous family name in the medical profession, taking on the broader modern responsibilities of that profession and of his role in the Mayo Clinic.

He moved increasingly into public service, giving generously of his time and concern. He supported the University of Minnesota in many ways. He was a board member and chairman of the regents. He served as an alternate United States delegate to the United Nations and as president of the American Association for the United Nations. Practically every nation in the world has conferred honorary degrees on Dr. Mayo. He was a member of many medical societies and associations and had been honored by universities all over the United States and the world.

Dr. Mayo was a gifted educator, author, editor and public servant. His accomplishments were many; his honors and recognitions too many to list, but perhaps the greatest of all, was Dr. Mayo's concern for individuals—their feelings, condition, rights and future.

LAWRENCE J. LEONARD, M.D.

Dr. Lawrence J. Leonard, 74, Minneapolis physician, died August 31. A native of Jordan, Minnesota, Dr. Leonard received his medical degree from Creighton University in Omaha and was licensed to practice medicine in Nebraska in 1916. He established a clinic in 1922 in North Minneapolis.

In the half century he served in the medical field, Dr. Leonard's special interest had bent toward allergies, gastrointestinal diseases, hypnosis and medical-legal problems.

Dr. Leonard was a member of the American Medical Association and the Hennepin County Medical Society and a 50 Club and Life Member of the Minnesota State Medical Association.

He is survived by his wife and one son, Dr. Lloyd F. Leonard.

NELSON W. BARKER, M.D.

Dr. Nelson Waite Barker, a member of the staff of the Mayo Clinic for 36 years, emeritus head of a section of medicine and chairman of two sections of medicine, died August 21, after a fall in his home.

Born on April 25, 1899, at Evanston, Illinois, Dr. Barker received his degree of doctor of medicine from the Rush Medical College of the University of Chicago. He came to Rochester in 1926 as a fellow in medicine.

Dr. Barker was certified as a specialist in internal medicine by the American Board of Internal Medicine, he was a diplomate of the National Board of Medical Examiners, a fellow of the American College of Physicians and a member of the Council on Circulation and the Council on Arteriosclerosis of the American Heart Association. He also was a member of the Minnesota Society of Internal Medicine, the Southern Minnesota Medical Association, the Zumbro Valley Medical Society and Associate Member of the Minnesota State Medical Association.

He was president of the staff of the Mayo Clinic in 1955.

He is survived by his wife, one daughter and two sons.

GEORGE L. BERDEZ, M.D.

Dr. George L. Berdez, 77, Duluth pathologist for 45 years, died August 19. A native of Lausanne, Switzerland, he was graduated from the University of Lausanne's Medical School and come to the United States in 1922.

He was the author of numerous medical books and papers on clinical pathology. Dr. Berdez was a member of the American Medical Association, the St. Louis County Medical Society, the American College of Pathologists, the Duluth Surgical Society, the Duluth Interurban Academy of Medicine and a Life Member of the Minnesota State Medical Association.

He is survived by five sisters.

JOHN F. ZACHMAN, M.D.

Dr. John F. Zachman, 39, Melrose physician, died August 26. He was born in Melrose and had spent most of his life in that community.

Dr. Zachman had a degree from the School of Forestry of the University of Minnesota but later entered the School of Medicine and received his medical degree in 1959.

He was a member of the American Medical Association, Stearns-Benton County Medical Society and the Minnesota State Medical Association.

His wife and two sons survive him. Dr. A. H. Zachman of Melrose is his father.

JOHN WILLIAM STUHR, M.D.

Dr. John W. Stuhr, 85, Stillwater physician, died July 30. Born in Euclid, Minnesota, Dr. Stuhr attended Macalester College and received his medical degree from the University of Minnesota in 1917. He interned at Ancker Hospital, St. Paul, and came to Stillwater in 1920 after serving as a lieutenant in the Navy Medical Corps in World War I.

He was a fellow of the American College of Surgery, a member of the Washington County Medical Society and American Medical Association and a 50 Club and Life Member of the Minnesota State Medical Association.

He is survived by his wife.

University of Minnesota

Minnesota Medical Foundation



Eivind O. Hoff, Jr.

An organization's growth is frequently the direct result of the initiative and foresight of an individual. This is true of the Minnesota Medical Foundation. An organization that has grown in the past eight years to a membership of 2,000 and which has acquired assets of five million dollars, the Foundation reflects the dedication and response to human problems exhibited by its present director, Eivind O. Hoff, Jr. The recent history of the Foundation is, for the most part, a tale of this man's personal managerial abilities and fund-raising skill.

The Minnesota Medical Foundation was chartered in 1939 to encourage private support of the University of Minnesota Medical School. In the succeeding eleven-year period membership more than doubled, from 415 to 851, and the Foundation accrued assets of better than $42,000. Up to that time, $81,000 had been donated through the Foundation for support of various

medical activities at the University of Minnesota. It was in 1959 that Eivind Hoff assumed the directive reins of the Foundation as the first full-time director. Thus began a new period of growth.

Mr. Hoff was a product of Mountain Lake, Minnesota, but received his high school diploma at Brainerd. After serving for a while as a U.S. Coast Guardsman, he entered the University of Minnesota, where he received the bachelor of arts degree in journalism, and then returned to active duty with the Navy for the latter part of the Korean conflict.

Mr. Hoff's communications career began in the world of sport—as sports publicity writer for the Minneapolis Park Board. In September of 1963 he moved to the position of publicity director for the Minneapolis Lakers basketball team. This "liberal education" helped him develop the art of dealing with news media during an era that was glamorous with the names and deeds of famous athletes.

The year 1955 saw Hoff moving from the Lakers and the sports world to the more sedate but ultimately equally exciting world of medical communications, where he assumed the responsibilities of public information director for the Minnesota Heart Association. It was here that Mr. Hoff encountered man's "most sensitive nerve," his pocketbook, and he insists he is still learning the techniques of extracting private monies for good causes. "It is decidedly not an exact science," he says. With the Heart Association, Hoff helped produce educational television programs on heart research for KTCA, Channel 2. Though he was the producer, he also found himself "acting" in some TV segments and is still seen occasionally in playbacks of these former productions screened for classroom viewing.

Mr. Hoff's potential was again challenged in 1959 when he was selected over 30 other applicants to serve as the first full-time director of the Minnesota Medical Foundation, a position created by the Trustees of the Foundation to implement its growth in new directions. His inventiveness served the Foundation well, as attested to by the growth figures in more than just dollars. He has been instrumental in implementing new programs and ideas, thus expanding the concept of the Foundation far beyond its original bounds of 1939. In 1959 the Foundation moved rapidly into fund-raising; into student relations; and, by means of activities coordinated with those of the Minnesota Medical Alumni Association, into alumni work. By 1961, membership dues from alumni and others were providing the operating funds of the Foundation, so that total contributions and bequests could go to the specific projects for which they were intended.

The Foundation has given nearly ten million dollars for Medical School purposes. Of its total assets as of June 1967, more than 85% were direct endowments. Today the Foundation grants more than one quarter million dollars annually for various purposes. The funds accrued through Mr. Hoff's diligent work and the activities of a dedicated Board have stemmed from a remarkable variety of sources throughout the Midwest and the United States. The $200,000 legacy of a North Dakota farmer now endows the Foundation's medical research program which encourages research by medical students and young faculty members. The construction of Diehl Hall, the new facility for the Bio-Medical Library, was aided through a gift of $25,000 from the Foundation. In 1967 a bequest from the estate of Royal A. and Olive W. Stone of St. Paul established an endowment for research in heart disease and cancer. The Foundation claims more than 3,000 alumni and lay members.

Mr. Hoff is also executive editor of the Medical Bulletin of the University of Minnesota, an alumni magazine which emphasizes strong ties among the Medical School's faculty and its graduates. "Keen interest in the Alumni Notes section of the Bulletin," says Mr. Hoff, "is an expression of latent affection for 'Alma Mater' which the Medical School must capitalize on." The Bulletin is circulated to more than 5,000 medical alumni of the University.

It is Mr. Hoff's opinion that the finest achievement of the Foundation is that of providing scholarships for medical students at the University. The first awards of $500 were granted in 1949. Through 1967, 678 scholarships totaling more than $330,000 had been distributed to deserving students.

Today the Foundation scholarship program assists 12% of the medical student body. Most of this money is expected to be contributed back to the school in future alumni gifts. Mr. Hoff predicts the time is not far distant when a Foundation scholarship will be available to every student in the Medical School. He also envisions the possibility of a tuition-free Medical School supported by the Foundation, certainly a worthwhile if perhaps somewhat unrealistically ambitious objective.

Personal contact is Mr. Hoff's forte. As director of the Foundation, he has established admirable rapport with administrators, medical professionals and students alike. His contemporaries are motivated by his inventiveness in making others feel ideas have originated within themselves. His office has become a meeting place for medical students seeking advice and counsel or just an ear to bend.

Through his many abilities and applied techniques, Eivind Hoff has done much to place the Minnesota Medical Foundation on a new level of service to the Medical School, to the University, and to the State of Minnesota. Its success is a story of his own goals and of those of the Medical School of the University of Minnesota.

Robert B. Howard, M.D.*
Minneapolis, Minnesota

*Dean, University of Minnesota Medical School.

Bloodletting Schedule

By the seventeenth century bloodletting had become pitiless. Guy Patin reports that he bled his wife twelve times for a fluxion* in the chest, his son twenty times for a continued fever, himself seven times for a cold in the head, and two friends thirty-six and sixty-four times each for fever and rheumatism respectively. The technique of the practice became highly specialized. Schedules of propitious times for bleeding were common from the days of Salerno. The list of appropriate days for bleeding recorded in the Bible of the Degge family of eighteenth century Virginia is:

"April, to let blood on the left Arm on the 3rd, 12th, or 15th, but the head of bleeding on the 7th, 8th, 10th, and 20th.

"May, This month to let blood on the 1st, or 8th, 10th and 27th, or 28th. But take heed of the 2nd, 5th, and 6th. It will be harmful.

"June, to bleed do it on the 28th day. Take heed not to bleed on 7th, 10th, 16th, 18th, or 20th."

And so on for the remainder of the year.†

*Fluxion—discharge.
†Bernhard Stern: Society and Medical Progress, 1941.

This advertisement for TAO® (triacetyloleandomycin), published at the request of the Food and Drug Administration, replaces a recent one which the FDA regards as misleading.

The advertisement headlined "new evidence for TAO . . ." and emphasized that the drug is "for the frequently seen respiratory infection in the office and for a problem pathogen* in the hospital. *Staphylococcus aureus."

We emphasize that triacetyloleandomycin is to be used only for acute, severe bacterial infections where adequate sensitivity testing has demonstrated susceptibility to this drug and resistance to other less toxic agents. In view of the possible, but reversible, jaundice and hepatotoxicity of this drug, other less toxic agents should be used unless the organism is resistant to those agents, or in those cases where hypersensitivity precludes their use.

TAO is contraindicated in preexisting liver disease or dysfunction, and in individuals who have shown hypersensitivity to the drug.

The advertisement emphasized that no tooth staining has been reported after ten years of use of this antibiotic. The Food and Drug Administration regards this claim as an implied comparison suggesting that triacetyloleandomycin and tetracycline have a similar antibacterial spectrum of effectiveness, and that TAO has less toxic potential. Any such implication is not intended and, of course, would be invalid.

The advertisement referred to a research study in which patients were given triacetyloleandomycin prior to determining the susceptibility of the offending organism. Any suggestion that triacetyloleandomycin be used clinically without first determining susceptibility of the offending organism should be disregarded.



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Not recommended for prophylaxis or in the treatment of infectious processes, which may require more than ten days continuous therapy. In view of the possible hepatotoxicity of this drug when therapy beyond ten days proves necessary, other less toxic agents should be used. If clinical judgment dictates continuation of therapy for longer periods, serial monitoring of liver profile is recommended, and the drug should be discontinued at the first evidence of any form of liver abnormality. When treating gonorrhea in which lesions of primary or secondary syphilis are suspected, proper diagnostic procedures, including dark-field examinations, should be followed. In other cases in which concomitant syphilis is suspected, monthly serological tests should be made for at least four months. When used in streptococcal infections, therapy should be continued for ten days to prevent the development of rheumatic fever or glomerulonephritis. The use of antibiotics may occasionally permit overgrowth of nonsusceptible organisms. A resistant infection or superinfection requires reevaluation of the patient's therapy. In the event such occurs with this drug the medication should be discontinued, and specific antibacterial and supportive therapy instituted.

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The James E. Moore Society

Origin and Purpose

THE JAMES E. MOORE SOCIETY traces back to discussions within the Department of Surgery approximately ten years ago. Since early post-World War II days the Department had sponsored a Quarterly Seminar in Surgical History—with Richard Lillehei's energetic, ardent, and wise leadership contributing to that effort. Each quarter of the school year 20 to 25 members of the Department assembled for dinner at the Campus Club and then repaired to the Mayo Auditorium for an evening lecture. In consequence, a keen and abiding interest in the History of Medicine was generated and took firm root in many of the Surgical Staff.

Student Participation

In time it became increasingly apparent that a similar function with active participation at the student level would have a potentially greater influence in creating within the Medical School a manifest and continuing interest in Medical History. It was J. B. Aust who crystalized deliberation into action and achievement in the school year 1961-62.

The student membership is a self-perpetuating organization, its participants chosen largely from the Junior Class in Medicine on the basis of scholarship, evidence of interest in Medical School matters beyond the required curriculum, and an affinity for Medical History and one another: constituting a fairly homogeneous group of the most talented and highly motivated students in the upper two classes of the School. This group of approximately 20 students meets once a month at the homes of faculty members of the Department of Surgery, joined by a few representatives of the staff. Dr. Mead Cavert, Associate Dean, has taken a keen interest in these sessions, and Leonard Wilson, Professor of Medical History, is providing enthusiastic support.

Choice of a Name

Anyone studying the history of the Medical School will quickly learn that a significant role in its development was played by Dr. Moore, a member of the Surgical staff from 1888 until 1904 when he became Professor of Surgery. He was essentially the builder of the Department—fervently interested in teaching and ambitious for the School's success and progress: a source of robust strength to the Medical School and the Department of Surgery.

Therefore it was with good reason that members of the Department of Surgery chose the name of James E. Moore to adorn this student organization with its special focus on Medical History.

Renewal of Interest in Medical History

Since student days a favorite theme of mine has been that if every teacher in the School from Anatomy to Zoology provided in his lectures a historical background of his subject matter, more effective teaching would result, since there is probably no keener incentive to scholarship in any discipline than a study of its evolution. Fielding Garrison has said that the best approach to Medical History is for the student "to back into it." What Garrison doubtless meant was that the student should not attempt to launch a systematic frontal attack upon the entire field but direct his maiden efforts at assessment of an isolated problem in a restricted area. Acquiring an acquaintance with the origins of the surgical procedures in my field made me, I feel certain, a more effective teacher than limiting my interest to the current scene. It has surprised and occasionally shocked me that some of our best students show little or only perfunctory interest in the literature of Medicine older than a decade and none for that prior thereto.

In recent years, however, there has been a gratifying resurgence of interest in Medical History among medical schools that hopefully will restore its teaching to the curriculum.

The James E. Moore Society is beginning to make its influence felt at Minnesota; its baptismal exposure to the fascination of Medical History should and undoubtedly will leave an indelible impress upon its participants. The time is not far off, I trust, when in both School and Community, in Gown and Town, there will arise a warm, palpable, flourishing interest in Medical History. That, after all, constitutes the most durable imprint and the most telling criterion of the success of the educative process.

Owen H. Wangensteen, M.D.*
Minneapolis, Minnesota

Editor's Note: With this issue a Student Section under the heading "The James E. Moore Society" will become a regular feature of MINNESOTA MEDICINE. A Student Editor has been appointed to the Board of Editors.

*From the Department of Surgery, University of Minnesota, Minneapolis.

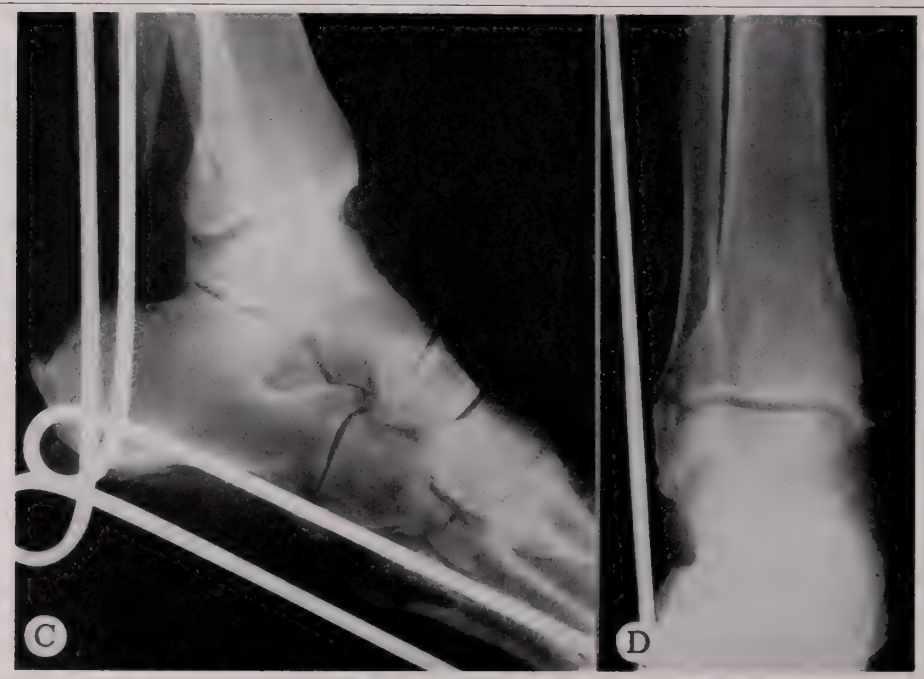


Fig. 1 C and D, After closed reduction. Reduction is acceptable. (See Fracture Conference, page 1386.)



NORTHLANDS REGIONAL MEDICAL PROGRAM

REGIONAL PROGRAM FOR HEART DISEASE, CANCER AND STROKE

Distribution of Physician Services

THE PROBLEM of the distribution of medical care personnel and facilities was brought into critical focus with the declaration by our society that modern medical services should be equally accessible to all persons. The Regional Medical Program Act was passed to stimulate better cooperative arrangements among health professionals to seek solutions to the problems of unequal medical care services.

Now that the fundamental duty of the medical profession to provide health care services to people has been re-emphasized, we need to analyze the nature of the problem of distribution. The cursory analysis described below embodies the following premises, which represent basic needs:

1. Functionally, the need for physician services may be assumed to be directly proportional to the number of people, the incidence of illness and death, and the number of hospital beds.
2. An unmet need exists for accurate morbidity data, but accurate data on the other parameters listed above are available.
3. The need for specialist services is greater in hospital practice and in areas with the highest death rates.
4. Occasionally, patients will travel long distances for medical services, but accessibility within reasonable driving distance is demanded for most services. Accessibility corresponds roughly with the economic subdivisions of the state.
5. People have come to recognize and demand the modern medical services and facilities which modern medical science has developed.
6. Recently, an inordinately large number of physicians (especially specialists) have located in or near large medical centers. Medical service problems are therefore intensified.

As a partial analysis of the problem, I have computed the following summary from available objective data:

	Medical Center Areas (7 County Metropolitan Area and Olmsted County)	**Remainder of State**	Area A (7 Counties NW Section)
% of Total Population	49	51	4.4
% of All Hospital Beds	56	44	4.6
% of All Deaths	43	57	5.1
Death Rate	7.9	10.2	10.75
% of All Doctors	68	32	2
Population per Doctor	650	1400	1979
Hospital Beds per Doctor	3.6	6	10.3

Deaths per Doctor per year	3.6	10	21
% of All Specialists	80	20	1
Population per Specialist	870	3500	6252
Hospital Beds per Specialist	5	15	56
Deaths per Specialist per year	7	36	67

The data for Area A (Northwest) show the greatest evidence of maldistribution, but those from Areas C, D and E (Central and Southwest) are similar. All peripheral areas show significant deprivation.

Deaths from heart disease, malignant neoplasms and cerebral vascular disease constituted 66.3% of all deaths, and the separate rates were proportionate to total rates in all areas. (1965 and 1966 data). The elevated total death rates show the increased need for all services in peripheral areas.

Specialists include all physicians claiming to be full-time in any specialty. (American Medical Association data.) The magnitude of maldistribution of specialists is clearly evident. Now that virtually all medical graduates specialize, the distribution problem may be expected to become progressively more acute.

Several uncontrolled variables are recognized: the younger average age of the population in the Medical Center Areas; the effects of patients coming from or going to out-of-state areas for medical services; physicians engaged primarily in administration, public health, industry, teaching and research; general practitioners who function as specialists. Quantification of these variables is fundamentally desirable. However, adjustment of the data from quantification of variables would probably not adequately explain the maldistribution. Specifically designed action programs are clearly needed to solve medical service needs.

What is the answer to this problem? . . . Production of more general practitioners? Development of new family practice specialists? Helicopter transportation of patients to large Medical Centers? Rapid transportation of Center specialists to peripheral areas? Development of rural extensions of large Medical Centers? Expansion of multidisciplinary group practices in towns which are economic area trade centers? Some of each of these?

How can we in the Medical Profession lead in finding solutions which will satisfy public needs and demand?

Winston R. Miller, M.D.
Program Director

Homo Sapiens

Men are very queer animals—a mixture of horse-nervousness, ass-stubbornness and camel-malice.—T. H. Huxley

---

This is another year when it won't be necessary to fool all the people all the time—only in the fall election campaigns.

What I mean is this—all good doctors must be primarily enthusiasts. They must have, like writers and painters, and priests, a sense of vocation—a deep-rooted, unsentimental desire to do good.—Noel Coward

---

The driver is safer when the roads are dry; the roads are safer when the driver is dry.



Meetings and Announcements

A wise man is strong; yea, a man of knowledge increaseth strength. Old Testament: Proverbs, xxiv, 5.

OCTOBER

Lyon-Lincoln County Medical Society
Clinical Sessions, October 1, 6:30 p.m., Chalet Club, Marshall.

Scott-Carver County Medical Society
County Society Meeting, October 1, 6:30 p.m., Wagner's Supper Club, Jordan.

Hennepin County Medical Society
Annual Membership Meeting, Pick-Nicollet Hotel, October 7, 6:00 p.m.

Nicollet-LeSueur County Medical Society
Dinner Meeting & Speaker, Dr. Bob Schmidt will talk on Pacemakers, October 7, 6:30 p.m., Holiday House, St. Peter.

Southwestern Minnesota Medical Society
Ellers Supper Club, Worthington, October 7, 7:00 p.m.

Brown County Medical Society
Fall Quarterly, Orchid Inn, Sleepy Eye, October 8, 7:00 p.m.

Lyon-Lincoln County Medical Society
Clinical Sessions, October 8, 6:30 p.m., Chalet Club, Marshall.

Camp Release District Medical Society
Hunt Hotel, Montevideo, October 10, 7:30 p.m.

St. Louis County Medical Society
Executive Meeting, October 10, 6:00 p.m., St. Mary's Hospital, Regular Meeting at 8:00 p.m.

Lyon-Lincoln County Medical Society
Clinical Sessions, October 15, 6:30 p.m., Chalet Club, Marshall.

Blue Earth Valley Medical Society
Interlaken Golf Club, Fairmont, October 16, 7:00 p.m.

Freeborn County Medical Society
Dinner Meeting, Albert Lea, October 17, 6:30 p.m.

Kandiyohi-Swift-Meeker County Medical Society
Westwood Inn, Spicer, October 17, 7:00 p.m.

Twin City Urological Society
Town & Country Club, October 18, 6:00 p.m.

McLeod County Medical Society
Velvet Coach, Hutchison, October 19, 6:30 p.m.

Minnesota Society of Internal Medicine, October 19, St. Paul.

Lyon-Lincoln County Medical Society
Clinical Sessions, October 22, 6:30 p.m., Chalet Club, Marshall.

Blue Earth County Medical Society
Century Club, October 28, 6:00 p.m.

Waseca County Medical Society, October 28, Regular Meeting.

Lyon-Lincoln County Medical Society
Annual Meeting, October 29, 6:30 p.m., Chalet Club, Marshall.

Goodhue County Medical Society
Semi-Annual Meeting, St. James Hotel, Red Wing, date & time not yet established.

Radiological Technologists Meeting

Minnesota Society of Radiological Technologists will meet October 11 and 12 at the Kahler Hotel in Rochester. Contact: James Powers, R.T., Mayo Clinic, Rochester.

A Program of Clinical Experience in Outpatient Education for Control of Diabetes Mellitus

The Diabetes Detection and Education Center, 916 East 15th Street, Minneapolis, Minnesota, has developed a program of medical and paramedical education for physicians, nurses, public health personnel, and dietitians. Classes are scheduled for the weeks of: July 22, August 5, August 26, September 9, September 23, October 7, October 28, November 4, November 18, December 2, December 16, and December 30. Rooms and meals are available at the Center at minimum cost.

For further information, contact D. D. Etzwiler, M.D., or C. B. Cohen, M.D., at the above address.

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THE WEST MEDICAL CLINIC has an opening for a General Practice Physician, on October 1, 1968. This is a five man group that conducts a practice near downtown St. Paul and also, has the Airport Medical Clinic at Wold Chamberlain Field, Twin City International Airport. Both clinics have full laboratory and x-ray services with technologists covering both fields.

The Airport Medical Clinic does industrial, occupational and Aviation medicine. FAA examinations are conducted at both clinics.

The clinic located near downtown St. Paul has a practice limited principally to internal medicine, pediatrics, as well as occupational and industrial medicine. There is only a limited practice of obstetrics and no surgery.

Salary is open and opportunity for partnership is available. Write: West Medical Clinic, 539 W. Seventh Street, St. Paul, Minnesota 55102. Phone: Area Code 612-227-9341.

WANTED: Physician for ward and/or clinic in accredited State Mental Hospital in fishing and hunting area of Minnesota. Should have interest though not necessarily experience in mental health and illness. Living quarters provided. Send vita with application. Not a retirement position. Older physician with good credentials acceptable. Write: MINNESOTA MEDICINE-414, 375 Jackson St., St. Paul 55101.

WANTED BY TWO INTERNISTS: A Board Eligible or Board Certified Internist to practice in the Twin City area. Excellent opportunity and early partnership. Write: MINNESOTA MEDICINE-407, 375 Jackson, St. Paul 55101.

WANTED: General practitioner to join two young general practitioners in well-established practice in suburban St. Paul. Excellent office space with lab, x-ray, and emergency room. Salary negotiable, with an association leading to early partnership opportunity. Write MINNESOTA MEDICINE 412, 375 Jackson St., St. Paul 55101.

FOR RENT: 14-room deluxe clinic in shopping center—Robbinsdale. 5 min. from Glenwood Hills and No. Memorial Hospitals—3 months rent free—will subdivide—36th Ave. No. and Noble—Noble Drug, JU 8-9449—Ben or Lou.

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ASSOCIATE urgently needed in busy general practice. Excellent clinic and hospital facilities. Salary open. Partnership after 1 year. Klefstad Clinic, Greenbush, Minn. Call collect: Lloyd H. Klefstad, M.D., Tele. 218—782-5275 or 4725.

DOCTOR WANTED in Fairfax Minnesota. Clinic building available. Present doctor leaving. This is an excellent opportunity. Please contact Dr. Glenn Nelson or Leo Keller at Fairfax.

DIRECTOR OF MEDICAL EDUCATION, full time —Methodist Hospital, St. Louis Park, Minnesota 55426. Contact Mr. Earl Dresser, Administrator or Dr. W. John Dawson, acting director of medical education.

FOR SALE: Rarely used manual Ritter Multi-purpose proctoscopic table—Model 3—Type 7. Purchase price when new $1,400.00. Best offer takes table. Telephone Mrs. Asmus 645-1195 or write Mrs. Asmus at 393 North Dunlap Street, 231 Central Medical Bldg., St. Paul 55104.

PSYCHIATRIST—board eligible, desires association with individual or group in Twin Cities area. Eight years experience in general and forensic psychiatry. Write MINNESOTA MEDICINE-413, 375 Jackson St., St. Paul 55101.

FAMILY PHYSICIAN wanted for an association with a clinic in the Minneapolis suburban area. Excellent hospital, school, churches, and living facilities available. Write Drs. T. J. Bloedel and H. R. Ransom, 226 Central Ave., Osseo, Minnesota, or telephone 425-2118 collect.

TWO MAN GROUP needs a third general practitioner in a fast-growing West St. Paul area. Begin with salary and assume early partnership. Contact N. W. Howe, M.D., or E. J. McEllistrem, M.D., 1246 Gorman, West St. Paul, Minn. 55118 Telephone: 224-8001.

GENERAL SURGEON, Certified, part or full-time association in multi-specialty clinic. Alfred F. Anderegg, M.D., 645-5851, 2500 Como Ave., St. Paul, Minnesota.

WANTED: G.P. to join clinic serving population area of 12,000. City has new hospital, new clinic building, two nursing homes, new Jr-Sr high school, new swimming pool, rich farming area in Red River Valley. Fishing and hunting nearby; metropolitan city close by. Salary open and partnership if interested. Write or call Warren Clinic, Warren, Minnesota 742-6231, area code 218.

GENERAL PRACTITIONER wanted to join well-established practitioner. New clinic building—90 miles east of St. Paul—city of 14,000. Early partnership with full hospital facilities. Ideal location. L. W. Picotte, M.D.; Chippewa Falls, Wisconsin.

PRACTICE AVAILABLE: A well-established general practice of 36 years in south Minneapolis with a well equipped office. Must retire because of physical disability. If interested phone 822-0493 after 7:00 P.M. any day, or write MINNESOTA MEDICINE 411; 375 Jackson, St. Paul, Minnesota 55101.

(Continued to Page 1477)

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(Continued from page 1475)

GENERAL SURGEON interested in some general practice to associate with a 2-man partnership in a rich agricultural community in southern Minnesota. Modern hospital and new clinic building. Hunting, 9-hole golf course, swimming pool. Salary open and full partnership as soon as desired. Write: MINNESOTA MEDICINE—405, 375 Jackson, St. Paul 55101.

WANTED General practitioner, to join two G.P.'s well established in north central Minnesota community 2200 pop., 65 miles from Twin Cities. Excellent office space with lab and X-ray, just opened new hospital all facilities. Assistantship or partnership. Considerable surgery and obstetrics. Hunting, fishing, golf club. Great opening for interested G.P. WRITE MINNESOTA MEDICINE—381; 375 Jackson. St. Paul 55101.

INTERNIST AND GENERAL PRACTITIONER wanted to join a five-man clinic group in Minneapolis. Complete laboratory and X-ray with board roentgenologist. Excellent hospital staff associations. Salary arrangement to start with, early partnership. Write MINNESOTA MEDICINE—289; 375 Jackson, St. Paul, 55101.

PRACTICE FOR SALE: Well established general practice in South Minneapolis serving an excellent community, within easy reach of the finest hospitals in the State. Very reasonable, low overhead. Splendid opportunity for solo or partnership practice. Write: MINNESOTA MEDICINE-397, 375 Jackson St., St. Paul 55101.

SKIING, HUNTING, FISHING and practice of Internal Medicine offered to board qualified or certified internist by 21 man specialty clinic in northern Minnesota. Presently adding new modern facilities to keep up with rapidly expanding economy. Salary first year, shareholder status second year. Reply Russell Anderson, M.D., East Range Clinics, Ltd., Virginia 55792 or call collect, Area Code 218, 741-6244.

GENERALIST as member of Medical Staff of progressive State Hospital in Michigan's Vacationland. Hospital has 3-year accreditation. JCAH and 3-year residency accreditation by A.P.A. Salary $17,867.20 to $21,777.60. Excellent fringe benefits. Civil Service security when qualified. Apply L. B. Young, M.D. Director of Medical Services, Traverse City State Hospital, Traverse City, Michigan 49684.

ST. PAUL: Spacious suite in new split-level building, partitioned for medical offices. Other level occupied by dentist. Excellent location adjacent to large shopping center. 1504 White Bear Avenue, 774-7144.

THREE MAN group in North West Wisconsin Resort, State Conservation and Retirement Area needs two more physicians adequately to serve their practice. Facilities offered are three-room physician suites, X-ray and lab under AMT technician, RN-only nursing personnel. New accredited thirty-two bed hospital and forty-six bed nursing home. Deer and duck hunting, fishing within five minutes of town. Internist most needed; generalists welcomed. Will meet any reasonable salary request. Partnership after one year. Write: MINNESOTA MEDICINE—365; 375 Jackson St., St. Paul 55101.

WANTED: G.P. or Internist willing to do some G.P. Twin-towns totalling 12,000 western Minnesota Group now two G.P.'s and one FRCS surgeon. Modern clinic building with eight assistants, X-ray and minor laboratory, 125 bed accredited hospital. Rotating calls one night a week and every fifth week-end. Hunting, fishing, golfing available. Initial salary $1,500 per month. Opportunity for partnership in one year. Apply to Louis T. O'Brien, M.D., Breckenridge, Minnesota.

FOR SALE: 200 N.A. 100 KV full wave diagnostic x-ray unit. Rotating anode tube. Pedestal control. Hand crank tilting table. Office equipment, instruments. Closing office. Contact Joseph F. Schaefer, M.D., 101 Main Street, Owatonna, Minnesota 55060.

JACK HEIMARK, Donald Freeman, Hobert Setzer, and John Eustermann would like to do more hunting, fishing, and traveling, and would appreciate sharing their time with additional Internists at the Mankato Clinic, Mankato, Minnesota. If you are Board Qualified or eligible and seeking a position, any of them would appreciate hearing from you.

FOR SALE: Busy general practice northern Minnesota. Ideal for 1 or 2 doctors. Clinic, 14 rooms with lab. and x-ray. Good community hospital. Fine home. Will introduce. Write: MINNESOTA MEDICINE—416, 375 Jackson, St. Paul 55101.

FOR SALE: (1) Kelley-Koeb 30 MA X-ray unit-table (tilting), fluoroscope, bucky plus all dark room equipment. (2) Portable x-ray unit with stand—for home (bedside) use. (3) 3 Unit sterilizer (gas operated)—water, instruments, dressings, etc. Phone or write Dr. A. J. Emond, Farmington, Minn. 55024. Tel. 463-8624.

PHYSICIAN NEEDED IMMEDIATELY: Present partner leaving 9/68. Prefer either general surgeon with GP experience, GP with general surgery experience, or GP-married and under age 46. Industrial town of 3500 economically unsurpassed located in NE Minnesota in Superior National Forest. Three large industries in town employ 2100 and I am only MD present. Practice consists of large private practice and treatment of industrial injuries. Clinic with complete modern facilities. High collection rate and very low overhead. Good housing available with no down payment required. Excellent income with many fringe benefits. Can get deferment. Unexcelled fishing-hunting-boating-camping-golfing-etc. Write with particulars or call after 6 pm. All replies will be kept strictly confidential. T. C. Leach MD, Babbitt, Minn. 55706, 827-6830.

BENSON & ASSOCIATES: Business & Professional Collection Specialists. No charge if no collection made. Pho: 888-2242, 8601 Nicollet Ave., Bloomington, Minn.

PHYSICIANS (Surgeon), (General Medicine), (Urologist), (Psychiatrist), wanted at 245-bed VA General Hospital in beautiful Black Hills area. Great all-year outdoor recreation offered. Requirements: Graduate approved school, licensed in any state. Salary based on qualifications. On station housing may be available. Nondiscrimination in employment. Contact Chief of Staff, VA Center, Hot Springs, S.D. 57747.

(Continued to page 1484)



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RE-6225

Minnesota State Board of Medical Examiners

Resolutions Adopted

on

July 12, 1968

BE IT RESOLVED, that Minnesota State Board of Medical Examiners proposes that the Rules and Regulations of Minnesota State Board of Medical Examiners be amended in the following particulars:

1. ME 2 (a), by striking and deleting therefrom the words "(which shall consist of both a written and oral or practical examination, as provided in ME 3)".

2. ME 2 (b) (2), by striking and deleting therefrom the words "oral or practical" and by substituting in lieu and in place thereof the word "licensing".

3. ME 2 (c), by striking and deleting therefrom the words "and who desires to take the oral or practical examination,".

4. ME 2 (e), by striking and deleting therefrom the words "both the written and oral or practical examinations" and by substituting in lieu and in place thereof the words "the licensing examination".

5. ME 3 (a), by striking and deleting therefrom the words "Examinations administered by the Board shall be both written and oral or practical.".

6. ME 4 (c), by striking and deleting the whole thereof.

7. ME 4 (d), by renumbering the same ME 4 (c).

8. ME 5 (c), by striking and deleting the whole thereof.

9. ME 5 (d), by renumbering the same ME 5 (c).

10. ME 11 (d), by striking and deleting therefrom the words "shall be both oral and written and".

BE IT FURTHER RESOLVED, that a public hearing on the adoption of the foregoing proposed changes in the Rules and Regulations of the Minnesota State Board of Medical Examiners be held on Saturday, November 9, 1968, at ten o'clock a.m., in Room 496 Lowry Medical Arts Building, Saint Paul, Minnesota.

BE IT FURTHER RESOLVED, that notice of such meeting shall be given by the Secretary of this Board pursuant to the provisions of Minnesota Statutes 1967, § 15.0412.

Bror F. Pearson, M.D.
President, Minnesota State Board
of Medical Examiners

J. P. Medelman, M.D.
Secretary-Treasurer, Minnesota State
Board of Medical Examiners



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Plan now to join your colleagues in Miami Beach. Be sure to look for the complete scientific program, plus forms for advance registration and hotel accommodations in the October 21st issue of JAMA.



Physician's Diary

Nothing is enough for the man for whom enough is too little.—Epicurus

Dr. James Cain, Mayo Clinic, is one of three new appointees that President Johnson has named to the Health Advisory Committee that works with the Office of Emergency Planning.

* * *

Dr. Robert H. Ransom, Osseo, was given the community service award presented annually by the administration and the board of trustees of North Memorial Hospital.

* * *

Dr. L. Emmerson Ward, chairman of the Mayo Clinic's Board of Governors, received the University of Illinois' Achievement Award at the University's commencement exercise.

* * *

Dr. Roger A. Johnson succeeded **Dr. Edward J. Engberg** as medical director of the Faribault State Hospital on July 1.

* * *

A distinguished Service Medal was awarded recently to **Dr. Carl M. Eklund,** Minneapolis, by the Secretary of Health, Education, and Welfare, Wilbur J. Cohen.

* * *

Dr. Jerome A. Hilger, St. Paul, has been elected as a vice-president of the American Academy of Facial Plastic and Reconstructive Surgery, Inc.

* * *

Dr. Franz H. Stewart of Miami has been appointed Editor of the Journal of the Florida Medical Association.

* * *

Appointments of ten new staff physicians, two associate consultants and two chief resident associates have been announced by the Mayo Clinic. The ten new staff physicians are: **Drs. Mark Cloutier** and **William Segar,** pediatrics; **John Merideth** and **Richard Van Dellen,** internal medicine; **Robert Garrison,** anesthesiology, **Keith Kelly,** general surgery and surgical research; **Robert Ryan,** endocrine research; **Richard Bryan,** orthopedic surgery; **Manfred Muenter,** neurology and **John Washington II,** microbiology. The two new associate consultants are **Dr. Andrew Lewis,** cardiology and **Dr. Eugene Turner,** pediatrics. The two chief resident associates are **Dr. Arthur Snyder,** general surgery and **Dr. Rafael Cohen,** chief resident in surgery assigned to Rochester State Hospital.

* * *

Gary Falk, Clarkfield, a senior at the University of Minnesota Medical School worked with **Dr. L. A. Syverson** for a month under a program sponsored by the Academy of General Practice established to give students first hand experience in general medical practice.

* * *

Dr. Earl Elkins, a senior consultant in Mayo Clinic's section of physical medicine and rehabilitation, has been named Minnesota's Physician of the Year for the second consecutive year by the Governor's Commission on Employment of Handicapped Persons.

* * *

Mayo Clinic obstetrician and gynecologist, **Dr. E. A. Banner,** has been elected president of the Continental Gynecologic Society at a meeting in Tampa, Florida.

* * *

Two urologists, **Drs. Joseph N. Aquilina** and **Charles H. Brady, Jr.,** joined the Mankato Clinic in July.

* * *

New Locations: Dr. John Marshall has opened up a practice in Pine Island. . . . **Dr. Harold C. Halvorson** has joined the staff of the Albert Lea Clinic. . . . **Dr. L. C. Strough** has joined the Worthington Clinic. . . . **Dr. T. P. Rohrer** who has practiced general medicine in Waseca for the past eight years, is leaving Waseca to further his studies at the University of Cincinnati Medical School. . . . **Dr. David Haldorson** of Duluth has joined the Warren Clinic. . . . **Dr. Fred Martin** has joined the Clearwater Clinic in Bagley. . . . **Dr. John Schotzko** has joined the Blue Earth Medical Center. . . . **Dr. David M. Armin** has joined the staff of the Community Health Center in Two Harbors and **Dr. Robert Nordberg** has joined the medical staff of the Broadway Clinic in Little Falls.

(Continued from page 1477)

PART TIME G.P. OR INTERNIST, 10 to 35 hours a week, examining predominently executive and professional personnel in a downtown Minneapolis medical building. Schedule quite adaptable, even on short notice. $15 per hour plus volume bonus. Write MINNESOTA MEDICINE—417, 375 Jackson, St. Paul, Minnesota 55101.

WANTED: GENERAL PRACTITIONERS, anesthesiologist, Urologist, Obstetrician, Orthopedist, & Pediatrician needed in growing community of 15,000. Service area 25,000. Present 83 bed general hospital. New 100+ bed automated hospital to be completed within 2 years. City has excellent industry, school system, and recreational activities. 45 minutes from Madison or Milwaukee. Future unusually promising. For more information contact: Administrator, Watertown Memorial Hospital, Watertown, Wis.

PUBLIC HEALTH PHYSICIAN—Positions available in local health departments for medical doctors with medical experience and training in public health. Salary range $20,000 to $25,000. Contact Mr. Roy Manty, Chief, Division of Local Health Administration, Department of Public Health, 3500 North Logan, Lansing, Michigan 48914. An equal opportunity employer.

PEDIATRICIAN and OPHTHALMOLOGIST wanted to join multi-specialty group in Virginia, Minnesota. Heart of the expanding taconite industry. Salary arrangement to start with, early shareholder status. Call or write Charles A. Tietz, M.D., Lenont-Peterson Clinic, Ltd., Virginia 55792, or call collect, area code 218, 741-4292.

EXPERIENCED GENERAL PRACTITIONER wants location in Twin Cities single or *small* group. Write MINNESOTA MEDICINE—368, 375 Jackson St., St. Paul 55101.

What's New?

New simple skin test for Histoplasmosis.

Lederle Laboratories recently announced the availability of a simple disposable skin test for the detection of Histoplasmosis infection. The test is performed using a stainless steel disc with four tines and the device is disposable. The advantages of the Histoplasmin Tine Test include convenience, ease of handling and low cost. The test is almost painless and its use in the physician's office should prove of great value.

Isuprel (Winthrop) is reported by a group of investigators to increase cardiac output at both normal pH and in the acidotic state. Reference, *Surgery* (63:181, 1968).

Schering Corporation reports to the profession that Tinactin (tolnaftate) is now available in a powder form. This new powder is a prescription drug and is available for those patients who may use it as effective method of maintaining the remission of fungous infection. The powder is packaged in a 45 gm. plastic container. Schering Corporation reports no side effects or contraindications.

Office laboratory procedures are said to be simplified with a new blood chemistry testing system developed by the **Dow Chemical Company,** Midland, Michigan. Advance information indicates that the system is applicable to hemoglobin, glucose, cholesterol, urea nitrogen, total bilirubin and uric acid, and testing time ranges from five to twenty minutes. The Dow Company invites requests for further information.

Minnesota Medicine at a Glance

Sulfonylurea Therapy—*Balodimos & Marble* Page 1341.

By evaluating diabetic angiopathy through the incidence of cardio- and peripheral-vascular disease, diabetic nephropathy and retinopathy, these authors were unable to identify any difference in the frequency of vascular disease between the use of insulin and that of an oral sulfonylurea drug.

Whipple's Disease—*Bornstein et al.* Page 1345.

Whipple's disease, previously considered uniformly fatal, now appears to be potentially curable with appropriate antibiotic therapy. The classic description of this condition represents the more advanced and terminal stages of the disease. A review of the reported cases suggests that the diagnosis could be suspected earlier on the basis of certain symptoms and findings.

A patient is presented in whom the clinical diagnosis of lymphoma had previously been made, but who failed to respond to cyclophosphamide therapy. Following a change in his clinical manifestations, the diagnosis of Whipple's disease was established. Of the earlier manifestations of this disease, nonspecific arthropathy may precede all others by several years; constipation may be the first or only gastrointestinal symptom; and hyperpigmentation of the skin may serve as an important clue to the early diagnosis of Whipple's disease. The diagnosis can be established by lymph node or small bowel biopsy when stained with periodic acid Schiff's reagent.

Esophageal Resection—*Peterson et al.* Page 1351.

Thirty-six cases of esophageal resection are present. Thirty were for malignancy, and of these seven are free of disease, four for over five years. Reconstruction is accomplished by transplanting the stomach up into the chest and anastomosing it to the remaining esophagus.

Clinical Reviews

A program of lectures and discussions on problems of general interest in medicine and surgery will be presented at the Mayo Clinic and Mayo Foundation, Rochester, Minnesota. Identical sessions are offered on October 28, 29 and 30 and November 11, 12 and 13.

This program is acceptable for credit by the American Academy of General Practice and the College of General Practice of Canada. The registration fee for this program is $20.

The number of physicians who can be accommodated is necessarily limited. For this reason identical programs will be offered two successive weeks. The program will be presented first on October 28, 29 and 30 and repeated on November 11, 12 and 13. Those wishing to attend should communicate with M. G. Brataas, Mayo Clinic, Rochester, Minnesota 55901, indicating which session they would prefer to attend.

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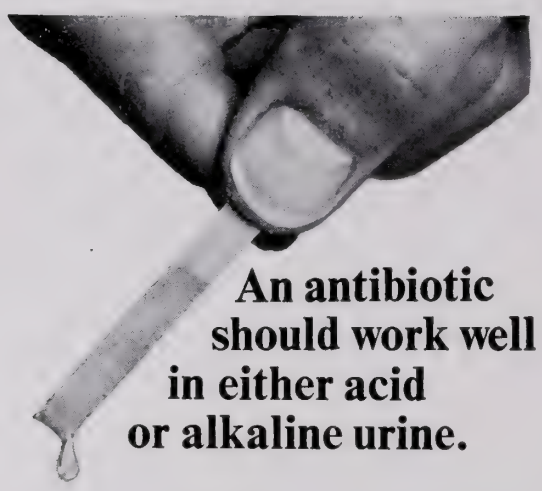

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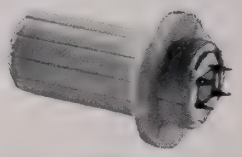
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See the President's Letter, Page 1493.

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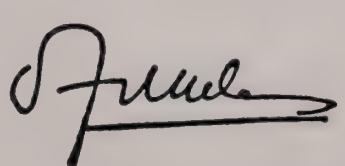
President's Letter

EARLY IN THIS century, no medical education was complete without post-graduate study on the continent. Doctor Howard B. Sprague, in his foreword to the George E. Fahr Festschrift, calls this "the Grand Tradition, the tradition of solid European training in the magnificent years before World War I." In speaking of Doctor Fahr, Doctor Sprague went on to say, "His is the tradition of the great teachers who brought back to the United States the knowledge and inspiration of the clinical and research giants." Indeed, Doctor Fahr did reminisce about his teachers—Max von Frey and Leube at Würzburg, Einthoven at Leyden, Siegfred Garten at Giessen, Adolph Weber at Bad Nauheim, Ascher at Bern, Volhard at Frankfurt, Krehl at Heidelberg, Romberg and Friedrich von Mueller at Munich, and Rudolph Straehelin at Basel. Common to these teachers and their schools was what Doctor Fahr used to call *"Lernfreiheit"*.

Now, in these pages, our German confreres from the Rheinische Friedrich Wilhelm Universitat, Bonn, West Germany, come to us, and we bid them welcome. Their land has named many stars to the medical firmament—von Bergmann, Paul Ehrlich, August von Wassermann, Robert Koch, Jakob Henle, Rudolph Virchow, Wilhelm Konrad Roentgen, and many more. As Sir William Osler has said, "It is one of our chief glories and one of the unique features of the profession that, no matter where the work is done in the world, if of any value, it is quickly utilized."

This literary visit of our German friends is a fitting example of the universality of medicine, "the only world-wide profession following everywhere the same methods, actuated by the same ambitions, and pursuing the same ends."

May we, in the future, receive similar visits from elsewhere on the globe.



O. L. N. Nelson, M.D.,
President
Minnesota State Medical Association

STATE MEDICAL ASSOCIATION

minnesota medicine

Volume 51

Number 11

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In prolonged therapy with penicillin, and particularly with high parenteral dosage schedules, frequent evaluation of the renal and hematopoietic systems is recommended.

In suspected staphylococcus infections, proper laboratory studies (including sensitivity tests) should be performed.

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Surgery of Gastric Carcinoma

PROFESSOR ALFRED GÜTGEMANN, M.D.*
Bonn, West Germany

THREE DECADES AGO (1938) Konjetzny spoke of "The Tragedy of the Stomach Carcinoma Patient." Today these words have the same tragic meaning if one realizes that about 25,000 citizens of the Federal Republic (West Germany) succumb every year to this disease.[27] In men this disease leads the mortality statistics, surpassing bronchial carcinoma and carcinoma of the genitourinary tract; in women it ranks ahead of carcinoma of the genital organs and of the breast.[7]

The history of surgery for gastric carcinoma shows periods of intensive endeavors in the developments of operative techniques followed by periods of resignation with regard to the postoperative prognosis. The doubts are based on the uncertain efficacy of gastric resections and especially of the more radical operative procedures, which carry a high mortality, even though this has been decreased with experience. *Much of the criticism has been directed against the presumably unavoidable and serious postoperative defect syndromes.*

It is a widely held belief that the price for prolongation of life is a so-called psychosomatic *vita minima* signified by agastric dystrophy[35] and by cachexia.

Knowing the history of gastric surgery it would be presumptuous to call present day developments a Renaissance of gastric surgery; still, surgery of the stomach is on the move. This applies to operations for peptic ulcer as well as for gastric carcinoma. In addition to curing the disease itself the operations are more and more designed to maintain the digestive synergism. In the surgery of peptic ulcer disease, for example, this has led to attempts to retain a sufficient gastric remnant, a residual acidity and an orthograde† duodenal passage.

Furthermore, there is apparently a causative potential carcinogenesis relationship in the type of resection and anastomosis for stomach ul-

*From the Department of Surgery, Director; University of Bonn. (Read at the Congress on Metabolism, Bad Mergentheim, October 22-23, 1966.)

†See Test Your Word Score Page 1583.

cers.[11] This was evident in comparing patients with Billroth-II- and Billroth-I-resections, where the incidence of gastric carcinoma in the stomach remnant was 2½ times larger in Billroth-II- than in Billroth-I-resections.[19,20] The incidence of carcinoma in the stomach pouch after Billroth-II-resections for ulcer was one in six, and the average period of latency was 21 years.[20] Achlorhydria and hyperplastic gastritis (transformation gastritis) developing after Billroth-II-resections in the stomach pouch apparently favor the development of a carcinoma.[47,49,71]

Aggressive eradication of the primary cancer, which threatens to involve the entire organism and ultimately kill the patient, is the only promising method of treatment of gastric cancer at this time. The problem of cancer surgery in the stomach is thus quite different from that of ulcer surgery.

The prognosis of surgically-treated stomach cancer depends largely upon the extent of resection. Radical removal must be striven for, since every attempt to retain the organ constitutes a heavy mortgage on cure. Even at operation it is not always possible to confidently determine the extent of the stomach carcinoma. Thus an assessment of the optimal degree of radical management becomes even more difficult. This, however, should not lead us to the conclusion that a curative resection is impossible in every case.

Mortality

The average stomach carcinoma patient dies approximately 5.5 months after the diagnosis has been established. The longest survival time without surgery has been 31 months. The patient who has undergone a resection—including operative mortality—can expect a four-times-longer survival time of 20.5 months.[27]

Subtotal Distal Gastrectomy

Let us consider the example of stomach carcinoma in the distal half, which is the most frequent site. A very impressive increase in five-year survival during the last six decades after an *extended subtotal distal gastrectomy* becomes evident. In three sequential series the absolute five-year survival rises from 7.1% to 16.1% to a present 29.1%.[3] This represents a four-fold increase. Other groups report similar improvements in results.[8,18,34,60,86]

One third of the patients with distal gastrectomy survived five years without recurrence, and further followup shows an increased life expectancy beyond the tenth postoperative year.[78]

Total Gastrectomy

Twenty percent of patients with carcinoma involving the entire stomach, treated in the past by *total gastrectomy* only, survived the fifth postoperative year. A followup of these patients also shows a considerable number of 10-year survivors without signs of recurrence.[24,25,26]

The absolute rate of resection for gastric carcinoma represents a measure of diagnostic reliability: the number of resectable stomach carcinomas divided by the total number of patients hospitalized for stomach carcinoma. The percentages during the three sequential periods in our institution rose for cancer in the distal stomach from 27.5% to 31.4% to 32.7% at the present time. They may be considered almost unchanged. The absolute rate of resection, however, rises to 40.1% and 44.2%,[78] if one includes total gastrectomy, which has become more frequent in recent years, and proximal gastrectomy for carcinoma of the cardia.

Advanced Operative Technique

The majority of patients with gastric carcinoma do not benefit from advanced operative techniques, nor do they show improved cure rates. Since it has not been possible to increase the number of resections by earlier recognition of the disease, our studies have led to two basic conclusions:

1. The development of advanced operative techniques in stomach carcinoma has resulted in great improvements.
2. The diagnostic effectiveness in stomach carcinoma, using clinical symptoms, laboratory findings and information obtained directly from the patient, has remained constant over the years. This disappointing but permissible conclusion is based on the incidence of resections and on the fact that nothing so far indicates a

change in the biological nature or the aggressiveness of gastric carcinoma.

The "early clinical diagnosis" is obviously complicated by the long period of latency in malignant degeneration, the biological viciousness of undifferentiated small cell carcinoma of the stomach, the frequent protean symptomatology, the problems of diagnosis, and the absence of unequivocal hematological and serological findings.[2] It is significant that the average time lapse between the patient's first consultation and the referral to the surgeon has been six months.[76,77] The complaints were too frequently attributed to a harmless gastritis, even after X-ray examination, although gastritis per se is quite rare. The complaints of dyspepsia all too often masked a carcinoma.

X rays

In reviewing previous X rays, it was frequently found that the early signs of carcinoma were either not recognized or were mistaken for gastritis. In spite of persistent dyspepsia some patients were not adequately followed clinically and radiologically, delaying the correct diagnosis. Sometimes the faith in an X-ray picture seems to be unshakeable.* On the contrary, the interpretation of an X-ray film should be influenced by the clinical symptoms. If there is a suspicion of carcinoma, further X-ray examination is called for.[22,40,62]

Surgical Principles In Carcinoma of the Stomach

Conventional Gastrectomy

The conventional gastrectomy for ulcer is confined to the skeletonizing of the lesser and greater curvature. Such a procedure would disregard the histologically recognizable extension of the cancer within the stomach wall.[14,57] Thus in relying upon the gross appearance one might believe that a circumscribed resection has been done within healthy tissue, and one might overlook carcinoma cell clusters in the remaining portions of the stomach which appear grossly to be uninvolved. This applies especially to the lesser curvature where about 85% of all stomach carcinomas appear.[27,45]

The conventional carcinoma resection has been found to be insufficient even when proven regional node metastasis is evident, as clearly shown in the fact that two thirds of the recurrences after subtotal gastrectomy originated on the lesser curvature side of the stomach pouch and one third in the remaining regional lymph nodes.[11,74]

Radical Gastrectomy

The principles of radical gastrectomy for carcinoma include the maintenance of[21] proximal and distal safety margins with resection through microscopically proven healthy tissue. In practice this is done by a stepwise, subtotal resection which includes the entire lesser curvature and sacrifices 80 to 90 percent of the stomach; the lesser and the greater omentum and all lymph nodes up to the coeliac axis should be removed in continuity by "en-bloc-resection" which includes the transection of the four main gastric arteries and removal of the contiguous lymph vessels and lymph nodes.

Types of Gastrectomy

If one includes the so-called cardia carcinoma which, by gross appearance, histology, and mode of extension, represents a carcinoma of the proximal stomach, there are three basic types of gastrectomy for carcinoma which correspond with the site and extension of the tumor: *distal gastrectomy* for carcinoma of the antrum or the lower corpus according to the principles discussed above,[24,25,26] *proximal gastrectomy* for carcinoma of the fornix and the corpus of the stomach including the cardia.[24,25,26] and *total gastrectomy*.[24,25,26]

Indications

The indication for gastrectomy[39,52] is always positive when: the carcinoma involves a major portion of the body of the stomach (especially of the lesser curvature) and it is impossible to maintain a safety margin of 6 cm; a diffusely infiltrating tumor with the histological picture

*"Denn was man schwarz auf weiss besitzt, kann man getrost nach Hause tragen."

What we possess in black and white,
We can in peace and comfort bear away.—J. W. Goethe, Faust.

Editor's Note: These words are spoken by the student to Mephistopheles who is masquerading as Faust. As for the context: Mephistopheles is confounding the student with specious and abstruse *metaphysics*, when what the student wants is definite *knowledge*.

of undifferentiated small cell carcinoma (carcinoma granulomatosum or a carcinoma gelatinosum) is found, since these tumors tend to have intramural extension which is difficult to recognize grossly; the tumor has metastasized beyond the primary lymph node drainage or if a so-called lymph node jump strip exists (however, only if distant metastases—lymphogenous, hematogenous, or intra-cavitary—are not present); the cancer involves the spleen, the left liver lobe, the pancreas, or the transverse colon, but is still resectable by an extended procedure.

Functional Impairment

Extended radical resections lead to functional impairment. Besides reconstitution of continuity of the digestive tract, the re-creation of a sufficient food reservoir is of particular importance.

Much concern over the advisability of radical gastrectomy and its sequelae has been voiced. At the same time modern cancer surgery has progressed far through a better understanding of the postoperative pathophysiology after radical gastrectomy and by the development of substitutional techniques.

Deficiency Syndrome

In the past an underestimation of the possibilities of radical cancer surgery, together with the observation that elderly patients show a markedly decreased adaptation to the newly created metabolic conditions, have led to a certain fatalism. This deficiency syndrome is invariably caused by lack of a nutritional reservoir leading to inanition, or to an accelerated upper intestinal passage, with incomplete utilization of the ingested food, which then leads to a malabsorption syndrome and to the so-called agastric dystrophy. Thus, all operative techniques which include the anastomosis of a too-small gastric remnant with the jejunum or the esophagoduodenostomy and esophagojejunostomy are functionally inadequate and hence unsatisfactory.

Physiologic Reservoir

In total gastrectomy or in all cases where the stomach pouch is smaller than 25 percent, creation of a new reservoir with sufficient capacity is required.[21,56,69] It is equally important to maintain the orthograde duodenal passage in order to insure a coordinated course of the digestive mechanisms located in the duodenum. We prefer the interposition of a jejunal loop between esophagus and duodenum of at least 25 to 30 cm in length after subtotal and total gastrectomies, either between the stomach pouch and duodenum or between the esophagus and the duodenum.[21,41]

Results

Our experience includes 136 such jejunal interposition operations: 120 after total, nine after proximal, and seven after distal gastrectomy.[3,27,78] The use of an isolated colonic segment[33] appears inadvisable, especially since the rationale for this procedure is based solely on animal experiments.

Metabolic Tests

Detailed metabolic tests performed on our patients prove that the interposed small intestinal segment, which functions as a stomach, fulfills its physiological tasks.[4,5,10] Besides the design and function of such operation, one has to take into account the objective and subjective symptoms in patients who undergo this procedure.[58,81,82] After a few weeks the fluoroscopy and cinematography show a good adaptation of the interposed small bowel loop to its new task: there is an elongation and dilatation of the loop which lies close to the left diaphragm and mimicks the position and shape of the stomach. This adapted small bowel loop serves as a reservoir for ingested food and as a mixing chamber as well.

Physiologic Propulsion

There is a physiological rhythm of food propulsion into the duodenum and into the upper small bowel which is an important prerequisite for an orderly course of digestive mechanisms. We have never seen in our patients any subjective or objective evidence of jejuno-esophageal reflux after small bowel interposition. Neither has there been any reflux esophagitis. We have, however, seen very bothersome reflux esophagitis on occasion in patients where the distal stomach stump was anastomosed to the esophagus.[58,73,79] Thus one might almost speak of a stomach-like transformation of the jejunal loop, which results in a sufficient ca-

pacity of the pseudo-stomach to permit the patient to resume his accustomed pattern of eating.

We know that a stomach which is too small leads to decreased food intake, culminating in apprehension and consequent starvation because the patient fears the symptoms which result from adequate food intake. By providing the patient with a stomach reservoir he can be adequately nourished; his entire nutritional and metabolic situation improves, and his attitude toward his disease and the newly gained life span improves progressively.

Digestive Function

Hydrolysis of the food proteins starts immediately in the interposed loop of small intestine through the action of regurgitated tryptic pancreatic proteases as well as the proteases produced by the bowel itself. Enzymatic protein cleavage and resorption of amino acids was checked by determining the level of amino acids in the serum during the fasting state and after a standard cottage cheese meal. Although the peak of amino-acid absorption appeared earlier and was found to be higher than normal, the total amount absorbed was found to be quite sufficient for all amino acids, including those which the body cannot synthesize. Total serum proteins and the electrophoretic pattern of serum proteins were normal after total gastrectomy and interposition of a small bowel loop. Immunoelectrophoresis showed neither dysproteinemia nor paraproteinemia indicative of nutritional or absorptive disturbances.[4,5,10]

Acidification

Besides the maintenance of an orthograde duodenal passage it is important to acidify the ingested food. This results in a pancreatic secretion rich in water and bicarbonates and poor in enzymes. One can thus avoid the precipitate proteolysis which occurs when pancreatic juice, rich in enzymes and poor in water, acts on the chyme and causes a speeded-up intestinal passage due to osmotic action.[33] Also the ionization of iron and calcium, important for their absorption, calls for acidity.[50,51] At last the ingested acid has a favorable effect on the microecology of the intestines.

Follow-Up

Substitution Therapy

Although the creation of a stomach substitute with an orthograde duodenal passage and fulfillment of physiological requirements induces favorable postoperative conditions, a long-term thorough followup is indispensable. Attention has to be paid to a sufficient intake of hydrochloric acid at meals and of bivalent iron, calcium, folic acid and vitamin B_{12}. A life-long substitution of vitamin B_{12} is absolutely necessary because of the removal of the gastric mucosa which forms the intrinsic factor.[65] One should also keep in mind the possibility of an exhaustion of the iron and calcium stores in the organism with consequent iron deficiency anemia or osteoporosis. These conditions can be either avoided or treated by an increased oral or parenteral substitution.

Feeling of Well-being

The value of gastric replacement procedures is borne out by the results in patients who undergo this procedure. The body weight remains close to normal. Freedom from symptoms and a general feeling of well-being leads in many cases to the resumption of work. After a period of adaptation of from three to 12 months, and in the absence of recurrence, any regimentation of food intake usually becomes unnecessary. Even in the absence of the stomach a sensation of hunger occurs at the usual times. It is of physiological as well as of psychological interest that one often finds in these patients a craving for certain foods which may not be easily digestible. For our patients we recommend a full diet rich in proteins, vitamins and minerals, and we discourage any type of special diets which in the long run are always starvation diets.

Conclusions

The application of the general principles of cancer surgery to stomach cancer results in more radical procedures and a better prognosis.

The dangers of starvation and of agastric dystrophy are overcome by maintenance of an orthograde duodenal passage and the preservation or creation of a sufficient food reservoir. This type of cancer surgery can benefit a larger

number of patients by increasing the number of curative resections.

Also beneficial is more extensive use of all modern diagnostic procedures, including X-ray examination, gastrocamera, gastroscopy, blind or open-mucosal biopsy in the stomach, cytologic study of gastric washings, and finally, increased use of exploratory laparotomy aided by histological examination.

Dyspeptic complaints are not characteristic and may herald an early stomach carcinoma. Only careful diagnosis and observation of patients with symptoms suspicious of gastric carcinoma will lead to more frequent recognition of the disease.

Finally, it is an important, albeit difficult, task to guide and follow a patient with gastrectomy after his hospital discharge. The incurable patient needs mostly psychological support, whereas the patient with a curative resection needs wholesome, nutritious food and substitution therapy as indicated by periodic laboratory determinations.

When a surgeon has occasion to resect a gastric carcinoma which was limited in size and had not metastasized beyond the area of resection, most of the praise should go not to him but to the physician who recognized the carcinoma early and refused to be misled by negative or questionable findings.

Throughout the past, recurrent periods of therapeutic resignation have been the main obstacle of stomach-carcinoma surgery. Anschütz said in 1914 at the 43rd Convention of the German Society for Surgery in Berlin: "I am glad to see more swing today in surgery of stomach carcinoma. For some time courage had waned. There were frustrating results. I believe that today's fine presentation of Herr Kuttner will animate us more and give us more confidence in resections. I suppose everyone will feel as I do when one follows the long-term results: I was surprised how many good results finally emerge."

From today's vantage point one should add that we now can recognize carcinoma earlier, that we can excise it with a better chance of success, and that in spite of extended resections we can make the postoperative existence worth living. Our experience of more than 15 years has shown that it is possible to compensate for the loss of the entire stomach by reconstructive substitution. Thus, in surgery of gastric carcinoma we can also observe the basic rule of all physicians, namely to heal more than to damage. The past reservations against the radical removal of gastric carcinoma should be abandoned.

Translated by: H. W. Heupel, M.D., Ph.D.

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He must have had a magnificent build before his stomach went in for a career of its own.—Margaret Halsey

Fibrinolytic Activity after Surgery*

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WHILE STUDYING the relations between surgical operations and fibrinolysis most examiners determined the fibrinolytic activity only during the first twenty-four postoperative hours. The main reason to examine the increase of fibrinolysis is to evaluate the fibrinolytic hemorrhages. Condurso[7] examined 30 patients immediately after surgery and found 3.3% complete lysis, but others[4,6,14,18,21] who examined their patients on the first postoperative day did not find increased fibrinolysis.

Thies[27] examined the fibrinolytic potential not only preoperatively and on the day of surgery but also on the first, third, fifth and eighth postoperative days. He determined the profibrinolysis-, antifibrinolysis- and fibrinolysis times[15] and the Heat-Fibrin[22] and found slightly increased fibrinolysis in seven out of 46 patients with minor or major surgical operations as well as in some accidents. He made his determinations four times: on the day of surgery and once each on the first, fifth and eighth postoperative days. No lysis was observed in the other 39 patients. The fibrinolysis content was always below 3%. The least fibrinolytic activity was observed on the third postoperative day (mean of evaluation of 32 patients). The author concluded that there is rarely an elevation of the fibrinolysis content postoperatively on the days which he used for evaluation. Similar results were reported by Tsitousis et al.[8] who examined the fibrinolytic action in 13 patients preoperatively and on the first, third and seventh postoperative days after major surgery. Using the lysis of a standard fibrin clot as the method, no spontaneous fibrinolytic activity could be observed. It can be said therefore that an increased fibrinolysis during the first postoperative week is a rare thing according to the results of the above-named authors. Up to now it has not been possible to demonstrate any definite changes in the postoperative fibrinolytic activity.

We intend now to observe the action of the postoperative fibrinolysis over an extended

*See editorial page 1579.

time and, in addition, to determine if there is possibly a decreased fibrinolytic activity. This problem has clinical interest since delayed fibrinolysis has been regarded by Stamm[25] as one factor in thrombogenesis.

Clinical-Experimental Examinations

The fibrinolysis tests were done on patients with thoracic surgery, because the lungs belong to the group of organs with a high content of tissue activator, as has been reported previously by different authors.[1,2,24,25,26] Zaman[29] found a surplus of plasminogen activator up to 20 hours postoperatively after lung resections, apparently originating from injured lung tissue. In addition there is a possibility that the lung may activate fibrinolysis by change to a more acid p-H (for instance in respiratory acidosis). Nielsson[19] and Schultz et al.[23] found increased fibrinolysis concomitant with decreased oxygen saturation of the blood. Some authors [8,13,17] also found an increase of fibrinolytic activity during metabolic acidosis.

Heart operations could induce activation of the fibrinolytic system, particularly when extracorporeal circulation is used for a long time or with the stress of replacement of blood or contact of the blood with artificial surfaces such as the heart-lung machine.

It therefore appears that heart and lung operations very likely may cause changes in the fibrinolytic system due to trauma during surgery and postoperatively due to disturbances of respiration and circulation.

The Problem

The following questions shall be examined:

1. Are there definite changes of the fibrinolytic activity during the postoperative course?
2. Is the extent of the changes dependent upon the kind of surgery? Particularly, is there a difference between thoracic and extrathoracic operations?
3. Are the observed changes of the fibrinolysis dependent on complications of respiration and circulation?
4. At what time after surgery are the changes of fibrinolytic activity most pronounced?

Type of Operations

The examinations were done on 38 thoracic operations. Controls were nine operations outside the chest.

Thoracic Operations

Type of Operation	Number
Lung	15
Heart with extracorporeal circulation	10
Heart in normal general anesthesia	10
Heart in hypothermia	3

Control Operations

Type of Operation	Number
Splenectomies	3
Laparotomies	2
Kidney	1
Thyroid	1

Method

The fibrinolytic activity was determined with the Euglobulin-Lysis-Time.[11] This method is preferable because of an easy technique, rapidity[5], a short observation time (two-to-four hours) and its sensitivity.[25] Samana and Yver[20] called the method the examination of choice in thoracic surgery because of the short duration of the test, the good correlation of its results with those of the thromboelastogram, and its ability to detect increases as well as decreases of fibrinolytic activity.

Euglobulin-Lysis-Time[11]

Principle

Precipitation of the Euglobulins with acid in citrate plasma causes the Albumin-Antiplasmins to remain in solution while all other fibrinolysis factors precipitate together with the Euglobulins. The Euglobulins are separated with centrifugation and removed, and a Euglobulin solution is made. This solution contains fibrinogen and clotting factors and can therefore be clotted with the use of thrombin. The time of the complete solution of this clot is the measure of the Euglobulin fibrinolysis. It represents the action of the present plasmin without the interference of the Albumin-Antiplasmins.

Normal Values of the Euglobulin-Lysis-Time

According to Kaulla and Schultz[11] the normal value of the Euglobulin-Lysis-Time

is between 120 and 240 minutes, or even a little longer. Less than 120 minutes is considered abnormal, representing increased fibrinolysis. Values of 50 minutes represent a marked acceleration of fibrinolytic activity; values of seven minutes indicate immediate danger of hemorrhage. Stamm[25] found that the lysis of fibrin with the Euglobulin fraction of normal plasma was usually completed in 180 minutes; values between 120 to 240 minutes were regarded as within physiologic limits.

In order to get a normal value for our method we determined the Euglobulin-Lysis-Time in 20 healthy persons (physicians, nurses, students, etc.). The values appear in the Table. A lysis time of 126 minutes was our mean value, with variations between 250 and 65 minutes. Nine of these lysis times were below the 120 minutes which by other authors were regarded as the lower limit. There were nine females and 11 males in this group. Age was between 20-30 years. The blood was drawn in the laboratory and the fibrinolysis determinations were done immediately in order to avoid loss of activity by storage of the specimen. There was a striking difference between the mean values in the female and male groups: the women had an average of 102 minutes, the men an average of 142 minutes. We do not have an explanation for this difference.

Results

Frequency of the Postoperative Determinations

The determination of the fibrinolytic activity was done during a two-week postoperative period in the first 10 patients with thoracic surgery and in the first three control cases. All other examinations were done during the third week after surgery. The examinations were done daily during the first week, every other day during the second week and twice during the third week. Precautions were taken to draw the blood without injury to the tissues in an effort to prevent a liberation of tissue activators of the fibrinolysis by using large blood pressure cuffs and large bore needles with polished lumen. Only siliconized syringes and canulas were used. A double fibrinolysis determination was done immediately and only occasionally was there a delay up to a maximum of 30 minutes.

The fibrinolytic activity after surgery was determined on 47 patients. A total of 452 determinations were made but only 250 were used because in these the dissolution of the fibrin clot could be followed to the terminal point. The results of our research are based on the evaluation of these 250 determinations.

The Mean Value

The mean value preoperatively in 13 patients was 175 minutes. Four of these patients showed a slight increase of fibrinolytic activity (100, 55, 110 and 65 minutes).

Absence of Correlation

None of the operated patients showed a postoperative increased fibrinolysis of clinical importance. Fibrinolysis was not increased (under 120 minutes) in 32 patients. In 15 patients (26 times in 250 examinations) there was a slight increase of fibrinolytic activity with lysis times under 120 minutes. There was no lysis time under 50 minutes. No particular age group was more involved than others. Sex did not make any difference; there were nine male and six female patients in this group. There was no relation to the amount of blood replacement the patients had received: some had received up to five times 250 ml, some less (up to 300 ml), and some did not have any blood transfusions at all. Also there was no correlation between postsurgical complications and increased fibrinolysis.

TABLE

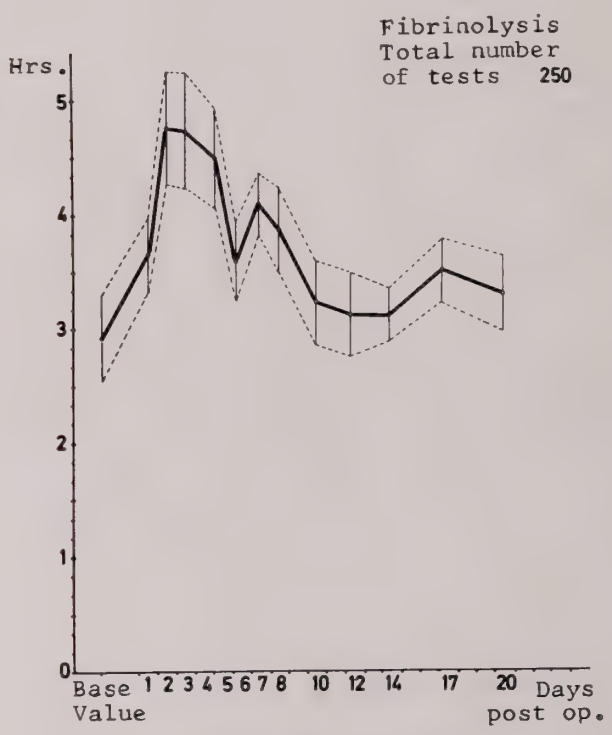
Normal Values of Euglobulin-Lysis-Time in 20 Normal Persons

No.	Sex	Lysis-Time minutes	No.	Sex	Lysis-Time minutes
1	male	135	11	male	250
2	male	135	12	fem.	95
3	fem.	65	13	fem.	120
4	fem.	80	14	fem.	110
5	male	155	15	fem.	70
6	fem.	75	16	male	70
7	male	125	17	male	200
8	fem.	170	18	male	105
9	fem.	135	19	male	115
10	male	200	20	male	120

No observation of a shortened lysis time was observed on any certain postoperative day or with any certain operation.

Postoperative Correlation

While the occasionally observed increased fibrinolytic activity appeared to be not characteristic, we found while evaluating the 250 single tests an obvious *decrease* of fibrinolytic activity (longer Euglobulin-Lysis-Time) during the first postoperative week, maximal between the second and the fourth postoperative days. The fibrinolytic activity remained decreased during the further postoperative course and returned only slowly to the starting values. Even three weeks postoperatively no normalization of the lysis was observed (Figure).



Figure

Discussion

Our starting value of 175 minutes Euglobulin-Lysis-Time correlates with the time reported by Stamm.[25] Slight preoperative increases of fibrinolysis have been observed before by other authors.[4,12] We found, as Thies[27] did, higher fibrinolysis potentials before than after surgery. The preoperative starting value was higher than the postoperative values up to three weeks postoperatively. Thies believed that psychic stress (fear of the operation) and preoperative hunger were responsible for this phenomenon.

The rarity of increased fibrinolysis during the postoperative course reported by Halse,[9] Thies[27] and Tsitousis[28] was confirmed up to three weeks postoperatively in our patients: there was no case of clinically significant increased fibrinolysis. The occasionally observed slight increase in fibrinolysis appeared to be unrelated to age and sex of the patient and unrelated to the kind of surgery. Thies came to the same conclusions. One may question if the observed increases in activity were just normal variations of the physiological fibrinolysis since similar values were found in healthy controls.

In the literature available to us we do not find any reports about an obvious decrease of the fibrinolytic activity during the first three postoperative weeks. The observed significant loss of activity on the second, third and fourth postoperative days is paralleled by the observation of Thies[27] that the smallest increase of fibrinolytic activity was seen on the third and fourth postoperative days in his 32 patients. He observed on these days the lowest profibrinolysis content, a normal antifibrinolysis content, an increase of the Heat-Fibrin and a decrease of the lysis of the fibrin clot, using the test tube method[15] with bovine fibrin. Thies[27] suspects a relation between the low tendency of lysis and the increased clotting tendency which has been shown by Markgraf and Hinrichs[17] to be present on the third and fourth postoperative days.

Conclusions

A decrease of the fibrinolytic activity of an obvious degree is noted during the postoperative time.

The amount of change is not dependent on the kind of surgery. There is no measurable difference of the fibrinolysis between intra- and extrathoracic operations.

We cannot report about a connection between postoperative complications and fibrinolytic activity because we did not encounter any serious complications with our patients.

The decrease of the fibrinolytic activity is particularly present during the first postoperative week. The greatest loss of activity is noted between the second and fourth postoperative days. A return of the Euglobulin-Lysis-Time to normal value occurred after the end of the third postoperative week.

Translated by: Henrich A. Dierker, M.D.

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A Family Doctor's Philosophy

It would seem logical, indeed, for a doctor to adopt a material outlook on life, since his business is the care and cure of bodies. I believe that all young doctors experience such a period in their growth. But as one grows older, the fierce denials fall away, and one begins to see that science needs spiritual guidance if it is to aid mankind on any road but a long fool's errand to the grave.

Being a creature of science disposes me more often than not to range myself under the banner of science, only to find that it will not do. As soon as I consider the wonders of the body, the miracles of the mind are forced on my attention; and if I rely on the mind, my hands reach for the instruments, since I have proved to myself, over and over, that they have their own special kind of wonders to perform.

How is it possible to separate the two? How can anyone say to me, "Faith or the knife, which will you have?" To him I answer that I will not choose. Too many times in my life I have been reminded that they are indissoluble, and no book on the subject, no ambitious partisan can make me change my mind. I choose both: faith in God and faith in man.*

*Joseph A. Jerger, M.D.: Doctor—Here's Your Hat! 1939.

Derivatively Speaking

Hyalin—from Greek *hyalos* (glass)

The hands that help are better far than lips that pray.—Robert G. Ingersoll

It's the Law

Primer of Parliamentary Procedure

"American Parliamentary Law is built upon the principle that rights must be respected: rights of the majority, of the minority, of individuals, of absentees, and the rights of all these together."*

"Primer of Parliamentary Procedure"† is written to present physicians with the fundamental principles of organized group action.

The Main Motion

Effective group action depends upon the introduction of new business in the form of a motion, a resolution or a committee report which initiates action. Such a matter may be brought before a properly organized meeting in one of several forms. A member may rise, be recognized by the chairman and state his views. Any other member who concurs may second the action. Then, when made in the proper form, seconded, and stated in full by the chairman the *main motion* is ready for consideration by the group. The fact that a motion has been made and seconded does not put it before the group, as the chairman alone can do this. The chair must either rule the matter out of order or state the motion so that the assembly may understand what is before it for consideration and action. At this point, and at this point only, can debate on the matter begin.

Immediately following the motion and the second, and before the motion is stated by the chair, members may suggest modifications of the motion, and the mover, without consent of the seconder, may make changes in the motion or even withdraw his motion completely. However, once stated by the chair, the motion must be disposed of by the assembly in a proper manner.

Having obtained a proper motion and second, the chairman simply states, "It is moved and seconded that we (stating the motion). Is there any discussion?"

Discussion or debate is now open to any member after recognition by the chair. Recognition in large assemblies requires the member to rise and address the presiding officer by his title, "Mr. President," or "Mr. Chairman" or "Mr. Moderator." Having been recognized by the chair, the member then gives his name and proceeds. In less formal groups, where all the members are known to each other, this identification is unnecessary and the chair may merely indicate recognition by facing or naming the member.

After debate is completed the chair puts the question to vote by saying, "The vote is on the motion that we (stating the motion). Those in favor of the motion say 'Aye;' those opposed say 'No.'"

During the debate or discussion the *main motion* may be modified, in one or several ways, and such alterations will be discussed next month.

Summary

1. A motion must be presented in proper form.
2. It must be seconded.
3. The entire motion must be stated by the chair before discussion or debate begins.
4. There can be only one *main motion* before the society at any one time.

John V. Thomas, M.D.
Duluth, Minnesota

*Robert's Rules of Order Revised, 75th Ed, 1951; Scott, Foresman & Co. Inc.
†Parliamentary Procedure at a Glance, O. G. Jones, 1949, Appleton-Century-Crofts, Inc.

(To be continued next month)

Etiology of Consciousness Disturbances in Surgery

C. KAUFER, M.D.*
Bonn, West Germany

SEVERE PHYSICAL ILLNESSES are often accompanied by psychic disturbances which merit special interest in surgery because of their frequency and grave prognosis. As symptoms they are of clinical value because they alert us to a general illness in the course of a surgical disease.[4] In surgery, disturbances of the mind are usually symptomatic psychoses and must be regarded as one of the symptoms of a known entity, though they are not necessarily an expression of the basic illness.

The most frequent and most impressive clinical symptom is a disturbance of the waking state. At times certain psychic derangements associated with an intellectual or emotional defect are manifested. A chronic loss of efficiency with personality changes is more rare. These aberrations may be reversible or irreversible; they may end with permanent defects, physiologic decerebration,† or even death. The psychic appearance is not necessarily determined by the nature of the underlying disease. For example, it is usually impossible to determine from the pathological symptomatology the exact type of noxious provocation,[1] since different physical illnesses may lead to similar psychic disturbances. The multiplicity of basic physical illnesses is in sharp contrast with the uniformity of psychic symptomatology.

Personal Investigations

Within a period of 10 months we have observed and analyzed 100 cases of serious derangements of consciousness at the Department of Surgery, University Hospitals, Bonn. However, this investigation is neither complete nor representative. One reason is that mild psychic alterations are easily overlooked in the routine of daily clinical work.[17,18] With increasing experience, however, we were able to properly evaluate certain symptoms which usually escape the uninitiated observer, and we began to recognize them as prodroma of mental disturbances.

*From the Department of Surgery, University Hospital, Bonn. Director: Professor A. Gütgemann, M.D.
†See Test Your Word Score Page 1583.

On the other hand, this investigation does not take into account cases of simple brain damage due to concussion or contusion; cases usually found in the accident wards, and of only minimal interest in the investigation of post-surgical mental derangements.

This account gives a general survey of the most frequent causes of mental disturbances in surgical patients (Table 1). Our patients underwent repeated clinical and psychopathological examinations. A number of standard laboratory chemical examinations were also made, and the particular phases of mental disease were repeatedly checked by brain-wave tracings. The neuropathological findings of those patients who died were available for comparison with the clinical course and proved to be quite valuable.

Somatic Causes of Symptomatic Psychoses

Our patient material permits subdivision with regard to causative factors, which proved to be illustrative and easily understood (Figure 1). In many cases of deranged consciousness it is impossible to pinpoint the somatic cause; in other cases a number of causative factors concur. For example, the question might arise whether a disturbed consciousness is caused by hemorrhagic shock following a ruptured spleen, by a simultaneous respiratory dysfunction due to aspiration, or by traumatic brain damage. Such a case exemplifies the possible interaction of different physical mechanisms. The multiple origins of disturbed consciousness, as described by Bleuler, have never failed to appear in our observations. However, we usually list the prevalent causative factor and elect to list multiple causative factors only if a retrospective analysis does not permit an exact pathogenetic classification.

Cerebral Disease

We have subdivided the organic diseases into *cerebral* and *extra-cerebral* disturbances (Table 2). These are mainly traumatic brain lesions either direct or indirect, or cerebral lesions caused by brain edema. The organic brain lesions are less frequent. Especially important in evaluating postoperative unconsciousness are the symptoms associated with vascular cerebral sclerosis which appear suddenly and defy immediate explanation. Frequently this condition is encountered following short episodes of hypotension. It is often difficult to separate this disturbance from brain metastases.

Respiratory Causes

Disturbances caused by respiratory factors are due to defects in the external respiration, i.e., mechanical derangements of respiration, tracheobronchial obstruction, or rib fractures; or they may originate within the lungs: disturbed alveolar ventilation, pulmonary emphysema, pulmonary edema, diminution of the respiratory surface as in pulmonary collapse, hypostatic pneumonia or atelectasis. Nor should a central respiratory depression and the consequences of an insufficient artificial respiration be forgotten.

Hemodynamic Factors

The hemodynamic factors which may give rise to a depressed state of consciousness in the surgical patient are hypotension, hypovolemia, shock of short or long duration, and all forms of cardiovascular dysfunction including circulatory arrest, thrombosis and embolism. Massive hemorrhage from accident as well as from elective surgery is a frequent

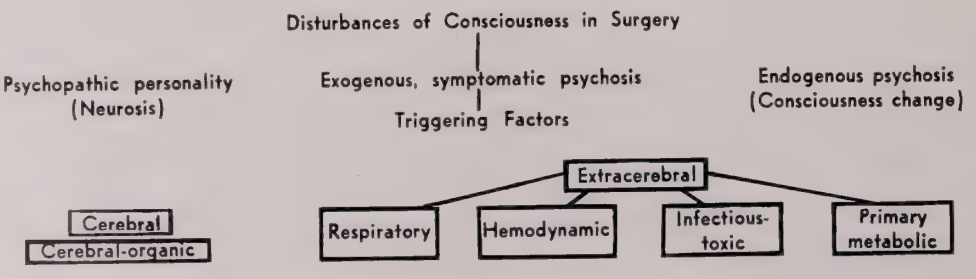


Fig. 1—Causes of consciousness disturbances in surgery.

TABLE 1

Consciousness Disturbances in Surgery
Department of Surgery, University Hospitals, Bonn, May 1966-March 1967

Endogenous Psychosis			
Cerebral-Organic		No.	Deaths
	Brain trauma	8	2
	Brain hemorrhage	1	1
29	Vascular occlusion	2	1
+34%	Fat Embolism	2	1
	Metastases	8	3
	Cerebral sclerosis	7	2
	Epilepsy	1	
Respiratory			
4	Respiratory insufficiency	1	1
+25%	Hyperventilation-alkalosis	1	
	Respiratory acidosis		
Hemodynamic			
	Hypovolemia	2	2
10	Cardiac arrest	2	
+33%	Perfusion damage	4	1
	Fibrinolysis	1	
	Cardiac insufficiency	1	

Infectious-Toxic		No.	Deaths
	Toxic	2	
26	Infectious—toxic	1	
+46%	Peritonitis	4	4
	Septicemia	6	5
	Tetanus	4	3
	Exogenous intoxication	2	
	Withdrawal—D.T.	7	
Metabolic			
	Hypochloremic alkalosis	2	
15	Hyperparathyroidism	1	
+40%	Renal shutdown	4	1
	Hepatic coma	8	5
Multiple Causes			
	Combined trauma & organic brain damage	6	
15	Combined trauma, organic		
+40%	brain damage—hypovolemia	3	2
	Combined trauma-toxic-organic brain damage	1	1
	Combined trauma & hypovolemia	1	
	Toxic cerebral sclerosis	1	1
	Respiratory hypoxemia	3	2

Total Number of Patients: 100
Mortality: 39%

TABLE 2

Consciousness Disturbances in Surgery
Organic Disturbance

Cerebral-Organic	Respiratory	Hemodynamic	Infectious-Toxic	Metabolic
1. Trauma, primary-secondary (Edema, conditioning)	1. Hypoxemia and hypercapnia (Compensated respiratory acidosis)	1. Diminished O_2 content of arterial blood (Anemia, cyanosis)	1. Inflammation	1. Hydration
2. Elimination of cerebral cortex	2. Decompensated respiratory acidosis and alkalosis	2. Diminished minute volume (hypovolemia, circulatory collapse, heart and vascular insufficiency, pulmonary embolism)	2. Endogenous intoxication (burns, ileus)	2. Electrolyte disturbances
3. Disregulation of sleep-awakening function		3. Circulatory arrest (Adams-Stokes-syncope, asystole, ventricular fibrillation)	3. Bacterial (endotoxin) (Peritonitis, empyema, septicemia)	3. Acid base imbalance
			4. Exogenous intoxication (listerol delirium)	4. Hepato-renal collapse
			5. Iatrogenous (Anesthesia, drugs)	5. Endocrine imbalance

cause. Fat embolism is not only followed by circulatory insufficiency, but it may also cause cerebral defects.

Infectious-Toxic Factors

Disturbances of consciousness of infectious-toxic origin may be caused by febrile infections, but especially by surgical complications such as wound infections, ileus, peritonitis, abscesses, phlegmony, empyema and septicemia (Figure 2). This particular group is of special interest to the surgeon because of frequency of occurrence as well as of its severe prognosis. In comparison with this group tetanus is now of secondary importance. The frequency of delirium due to alcohol withdrawal is surprisingly high.

Chemical Imbalance

Fluid and electrolyte imbalance as well as acid base derangements may be considered metabolic in origin (Figure 3). Further metabolic derangements are liver diseases and renal insufficiency, especially primary liver or renal disease with subsequent hepatic encephalopathy and liver coma or with uremia. Parenchymal disease with the danger of hepatorenal insufficiency may be considered a surgical complication. Endocrine disease with metabolic coma also belongs in this group.

Discussion

Our observations indicate that a number of diseases may lead to disturbances of consciousness. Although the causative factors may be known, they do not explain the pathogenesis. All derangements of consciousness are basically central events.[13] A diffuse destruction to the cortex may lead to derangement of consciousness.[9] In these cases there is a relationship between consciousness and the frequency of discharge from the cortical neurons.[3] Most extra-cerebral mechanisms cause such hypometabolism of ganglionic cells. Another group of consciousness disturbances may be caused by an upset of the sleep-wakefulness mechanisms located in the brain stem.[9]

The histopathological findings are merely in-

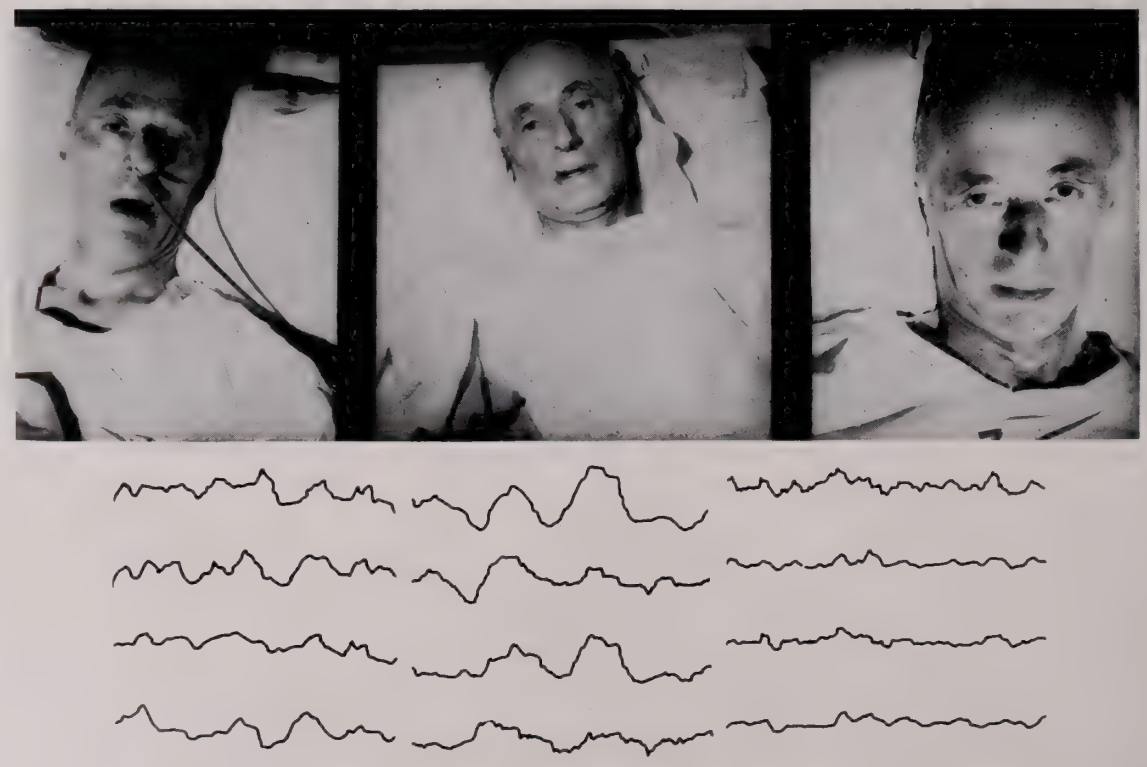


Fig. 2—Symptomatic psychosis in a 63-year-old with ileus and peritonitis. (a-left). Paranoid-hallucinatory transient syndrome with mild impairment of state of wakefulness. Electroencephalogram: Mild general changes. (b-middle). Acute mental disturbance. Electroencephalogram: Delta-rhythm, grouped (delta parenrhythmia). (c-right). Reversion in amnestic-affective transient syndrome. Electroencephalogram: Border-line mild general change.

dicative of local circulatory impairment.[13] These histological changes are caused by hypoxemia or by deficient cell nutrition or deficient elimination of waste products.[11] Chronic states of hypoxemia do not usually lead to cell death and necrosis but result in diminished cell volume, especially in certain centers, the so-called topistic units.[21]

Traumatic Brain Damage

A brain damaged by trauma or disease is very sensitive to any additional limitation of oxygen or energy supply.[8] While relatively slight noxious effects have no detrimental result on consciousness and brain function in the normal person, they may lead to disturbances of consciousness or even death when they act

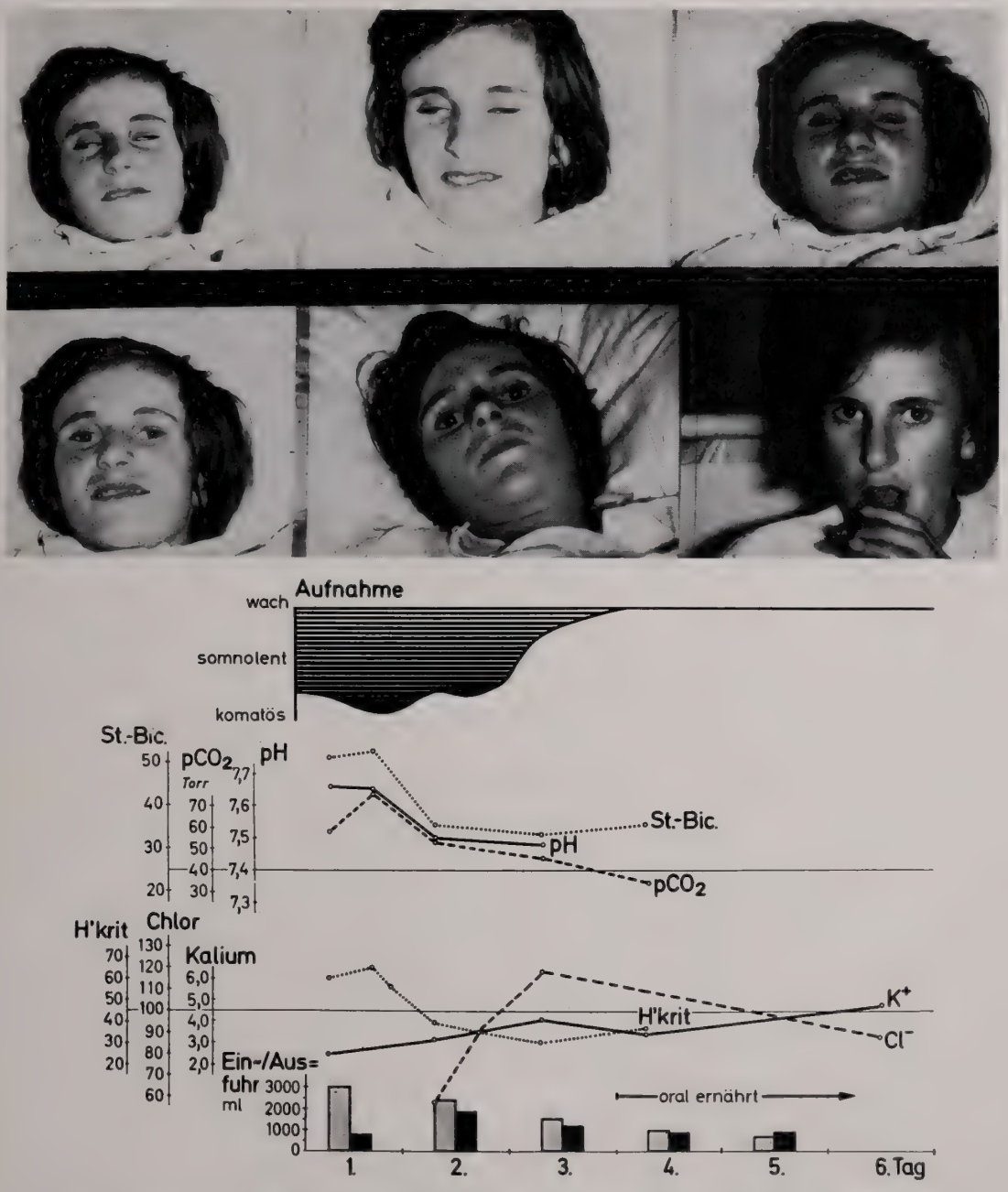


Fig. 3.—Observation during the course of an acute consciousness disturbance in hypochloremic-hypocalcemic alkalosis with dehydration following gastric-atony and fluid loss after blunt abdominal trauma in a 13-year-old girl. Clearing of consciousness and healing after correct substitution.

upon a brain of augmented vulnerability. Aside from direct cerebral damage a skull-brain trauma thus conditions the brain for secondary damaging effects as has been demonstrated by Selye for other diseases. In some instances we have seen how minor skull damage led to disturbances of consciousness in cases where a preceding brain injury had apparently been overcome. Furthermore, a simultaneous skull and brain injury may mask trauma to other organs and cloud their symptomatology.

Respiratory Insufficiency

Disturbances of consciousness in respiratory insufficiency are not so much the immediate consequence of hypoxia as that of respiratory acidosis or alkalosis. In these cases a relationship between the partial CO_2 pressure and the pH of the arterial blood is apparent to the changes of the consciousness level.[5] These derangements of the consciousness level obviously appear when the cerebral circulation (which depends on the systemic blood pressure) falls below a critical value or the oxygen content of the blood drops drastically for short periods of time.[15] A short period of ischemia acts more promptly and more profoundly than anoxemia.[13] The cerebral circulation may be insufficient in the presence of persistent heart action.

Infectious-Toxic Derangement

The pathogenesis of infectious-toxic derangements of the consciousness level is complex. Even simple infections lead to changes in vascular permeability for which histamine-like substances may be responsible. A serum permeability factor has been isolated.[22] While bacterial exotoxins do not lead to disturbances of the conscious mind,[12] endotoxins are known to cause cerebral swelling, hemorrhage, thrombosis and vascular damage.[2] Fever per se is not considered the cause of acute psychoses.[12] Alcoholic withdrawal delirium was found surprisingly frequently among our patients, at times with classical psychopathological and electroencephalographic symptoms. These patients demand special attention on account of their threatened secondary metabolic complications and the danger of infection. Fortunately our mortality in this group was less than the 30% reported by Tasca.

Chemical Imbalance

Water and electrolyte imbalances are most often the consequence of other diseases and rarely the primary defect.[6] Potassium deficiency states may be mentioned whose relationship to postoperative psychoses has been pointed out recently by Schwaiger and Staib.

Hypochloremia, even of moderate degree, may lead to derangement of the consciousness level. A number of metabolites have been implicated in the pathogenesis of hepatic coma, although a strict correlation has not been found.[10] There is a correlation between hepatic uremic disturbance of consciousness as evidenced by clinical findings and by biochemical investigations with acetoin and butylenglycol elevations.[20] A definitive diagnosis of metabolic coma due to endocrine derangement depends largely on the clinical symptomatology.

The two leading causes in the pathogenesis of unconsciousness are lack of oxygen and defects in the utilization of glucose, since the brain metabolism depends almost entirely on the oxidation of glucose.[7] Basically, all disturbances of the consciousness level are caused by a dysfunction of the cell membrane and of the cell itself. The high mortality of 39% in surgical patients with derangement of the consciousness level demonstrates the importance and the severe prognosis of this complication. Every disturbance of the state of wakefulness which occurs in the course of a surgical illness aggravates the prognosis.[4] One abnormal laboratory finding alone does not necessarily indicate a disturbance of the consciousness level or of the psychic behavior. These disturbances are usually the consequence of a complex derangement caused by a number of factors. Repeated examinations with determination of important functional entities and especially clinical experience provide the prognostic clues. The physical cause, often a surgical disease, must be found. Only complete correction offers the possibility of cure.

Summary

Disturbances of the consciousness level are alarming signals. They occur in the course of surgical diseases and have, in our experience, a mortality of 39%. The somatic causes for a

symptomatic psychosis are numerous. The etiology includes organic brain damage: respiratory, hemodynamic, infectious-toxic and primary metabolic causes. The pathogenesis is usually complex, combining a number of factors. Cerebral hypoxemia and disturbed glucose utilization of the brain are of special pathogenetic importance.

Translated by: H. W. Heupel, M.D., Ph.D.

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Prayer of a Discouraged Young Man

Lord, I call unto thee from the depth of my disheartened spirit. My will wavers and falters and fails. My hopes of yesterday, so buoyant and so brilliant, today have ended in the ashes of disappointment. My plans are cruelly thwarted. I am beaten by the buffetings of life and scarcely can find the strength in my hands and the resolution in my heart to take up again the broken threads of effort and of ambition.

Buttress, O Lord, my wavering will. Give fire and life again to my flagging hopes. Show me that the plan which failed today will but gird me for a wiser plan tomorrow. Enable my heart to see that my buffetings may but beat into me a greater strength. Nerve thou my flagging hands and enable me again to reach forth gladly for the toil and the gifts of life.

And above all, give me wisdom to see that my only final failure will be within myself, and that if my spirit fails not, I have found success. Amen.

P. R. Hayward

Draft Board Classification

In spite of the emphasis being put on bodily fitness for military service, it is not the thing America needs most. To develop military and naval geniuses is more important for the national security. There is no formula for this, but physical fitness is not necessarily the key. Many of the world's greatest military figures would have been rejected by the draft boards for these reasons:

George Washington, false teeth; Bismarck, overweight; Napoleon, ulcers of the stomach; U. S. Grant, alcoholism; Julius Caesar, epilepsy; Horatio Nelson, one eye, one arm; Kaiser Wilhelm, withered arm; Duke of Wellington, underweight.*

*Dr. Logan Glendening, Nation's Business.

What fools indeed we mortals are
To lavish care upon a car,
With ne'er a bit of time to see
About our own machinery.—John Kendrick Bangs

The School of Salernum*

Traveling southeast from Naples in sunny Italy one arrives at the attractive and lively Tyrrhenian seaport of Salerno, dating back in proud antiquity to ancient Salernum, an early Roman health resort and subsequent site of the first medical school, the School of Salernum. Wandering into the "old" section of the historic town one might, with sufficient imagination (there are no identifiable ruins), recapture the aura of Civitas Hyppocratica, which flourished for centuries, reaching its pinnacle of fame and glory in the 11th and 12th centuries.

How the School became the apotheosis of medical wisdom is a familiar and fascinating story: the medieval phenomenon of eclecticism whereby scattered and isolated cultures gravitated to favorable centers to pool their individual contributions. Salernum became such a center: medical savants from all over the then civilized world congregated to share and amalgamate their knowledge. It has appropriately been said that the School was founded by a Latin, a Greek, an Arab, and a Jew, thus becoming the collector, repository, and transmitter of the best medical wisdom then extant.

Students flocked to Salernum from near and far to observe and learn. A constant stream of patients came and went, the bulk of them Crusaders with the multifarious diseases and injuries acquired on their pilgrimages to and from the Holy Land.

Just as any Mecca becomes a magnet, so did the School of Salernum.

The magnum opus of that illustrious period was the Regimen Sanitatis Salerni, composed by the doctors of the School to serve as a directive for physicians and a handbook of home medicine for the layman. Its manifest objective was to motivate its lay readers to respect professional advice (if they could get it), to use common sense in self-prescribing and treatment, and to divest themselves of medical superstitions.

In tone the Regimen is alternately serious and jocular, naive and sardonic—with an occasional malicious jibe at physicians for their pedantry and laymen for their adherence to folk fallacies.

In literary form it is a collection of succinct Latin aphorisms, brilliantly translated into 16th-century English by the distinguished Elizabethan poet, Sir John Harington, who has so consummately captured the blithe spirit and ineffable charm of the original.

The quintessential quality and flavor of the Regimen is invested in a single couplet:

"Use three Physicians still; first Doctor Quiet,
Next Doctor Merry-man, and Doctor Dyet."

Editor's Note: This introduction will be followed in subsequent issues by extracts and analyses from the School of Salernum.

Law

When I hear any man talk of an unalterable law the only effect it produces upon me is to convince me that he is an unalterable fool.—Sydney Smith

---

He looked at me as if I was a side dish he hadn't ordered.—Ring Lardner

Portal Hypertension Varicose Vein Bleeding and Shunt Operation

PROFESSOR GÜTGEMANN, M.D.*
GREGOR ESSER, M.D.*
Bonn, West Germany

IN 1751 GEORGE ERNST STAHL described correctly in his doctor's thesis, entitled "De vena portae, porta malorum," the syndrome of portal hypertension in liver cirrhosis. More than one century later this disease attracted the attention of surgeons when the preliminary animal experiments of Nikolaus Eck became known in 1877. Lenoir in France performed the first portacaval anastomosis in a patient with decompensated liver cirrhosis, for alleviation of ascites. Vidal, in 1903, was the first to recommend portacaval anastomosis for the treatment of bleeding esophageal varices, at the 16th French Congress of Surgery. One patient operated by him in 1904 for ascites survived; however, it recurred after six weeks. Rosenstein in Germany had the first lasting success in 1912 in treating ascites with portacaval anastomosis in a 60-year-old woman.

There were scattered reports of this operation in the following years: by Kleinschmidt in 1935 and Jusbasic in 1939. Portacaval shunt operations were finally firmly established and publicized with the successful work of Whipple, Blakemore and Lord for the therapy and prophylaxis of varicose-vein bleeding in portal hypertension.

This report is based on experience of the last fifteen years with 725 patients suffering from portal hypertension, on whom + 353 portacaval shunt operations were performed.

Etiology

Intrahepatic Blocks

The vascular occlusion within the liver and the so-called intrahepatic block is an unsatisfactory explanation; for, when the portal vein is transected at its entrance into the liver and then anastomosed end to side with the vena cava, neither does the pre-sinusoidal pressure become normal despite a 60 percent reduction of the blood supply to the liver, nor is there a return to normal blood pressure in the epiploic

*Department of Surgery and Policlinic, University of Bonn. Director: Professor Alfred Gütgemann, M.D.

veins which are presumably decompressed.

Liver Cirrhosis

The main cause of portal hypertension is liver cirrhosis. The underlying disease, however, differs with geographic location and social status. In the United States 60 to 80 percent of cirrhoses are caused by alcohol abuse, and the figure in France is 80 percent. In our area alcoholic cirrhosis accounts for 15 to 20 percent, while post-hepatitic cirrhosis is responsible for 80 percent.

Bilharziosis

Bilharziosis is the prevailing causative liver disease in certain regions, especially in Egypt, Mesopotamia, Madagascar, Brazil, Venezuela, Japan, China, Formosa, the Philippines and Indonesia. It is distinguished by two factors: (1) the hepatic parenchymal tolerance in bilharziosis is considerably greater than in alcoholic-toxic or post-hepatitic liver cirrhosis, and (2) the portal-hypertension in bilharziosis of the liver causes a pre-sinusoidal block as contrasted with the post-sinusoidal block in liver cirrhosis.

Hepatitis

There has been a steady increase in the incidence of hepatitis in our part of the world. About 10 years ago the incidence of hepatitis without jaundice was estimated as 20 percent of all hepatitis cases. Systematic investigations during the last few years revealed a percentage of 40 to 60 percent. The incidence of liver disease approximates that of diabetes. Burgmann estimated in 1963 the annual number of fatal hemorrhages due to liver cirrhosis in Germany as 3,500. Considering this figure, the number of operations performed must be considered small, in our area as well as in the rest of the world.

Complications of Portal-Hypertension

Varicose Vein Bleeding

Varicose vein bleeding, the most serious complication of portal hypertension, makes it a surgical disease. About 40 to 60 percent of all patients with liver cirrhosis develop portal hypertension, and approximately 60 percent of these bleed from varicose veins.

Rate of Survival of Bleeding Esophageal Varices in 200 Treated Cases

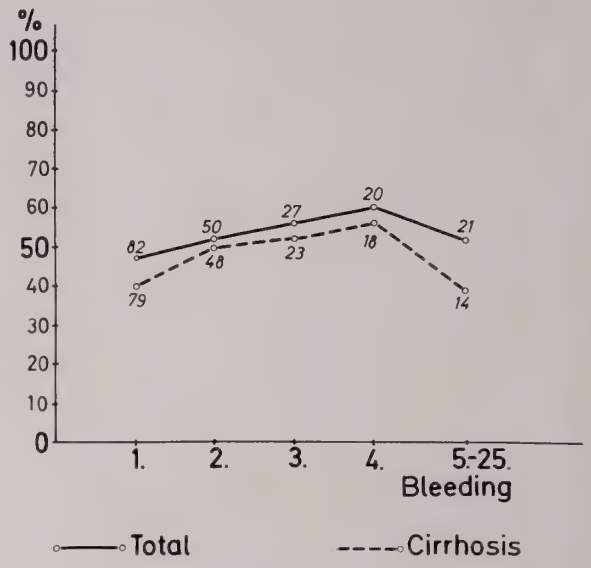


Figure 1

Causes of Death in Acute Bleeding of Varices (102 Cases)

	Number
Bleeding *	50
Livercoma	34
Secondary Failure of the Liver	3
Heart or Circulation Failure	7
Pulmonary Embolism	4
Septicopyaemia	1
Pneumonia	1
Peritonitis	1
Livercarcinoma	1

* in Connection with Livercoma 21, with Precoma 2

Figure 2

Pre-hepatic and post-hepatic vein obstructions are responsible for portal hypertension in approximately 15 percent. Acute hemorrhage from varicose veins due to liver cirrhosis is always a life-threatening event. Of all gastrointestinal bleeding it carries the worst prognosis.

Hepatic Coma

The aggravating factors to increase the danger of hepatic coma are: (1) the usually huge blood loss; (2) the early failure of autonomic compensatory mechanisms in a state of acute low blood volume; and (3) the sensitivity of the damaged liver to hypoxia. In this state of circulatory centralization the liver acts as a peripheral organ.

The surviving rate from acute hemorrhage in relation to the number of bleeding episodes is shown in Figure 1. The prevailing causes of death are hemorrhage and hepatic coma (Figure 2). The mortality of acute varicose vein hemorrhage as reported in the literature is shown in Figure 3.

Mortality in Acute Bleeding of Varices

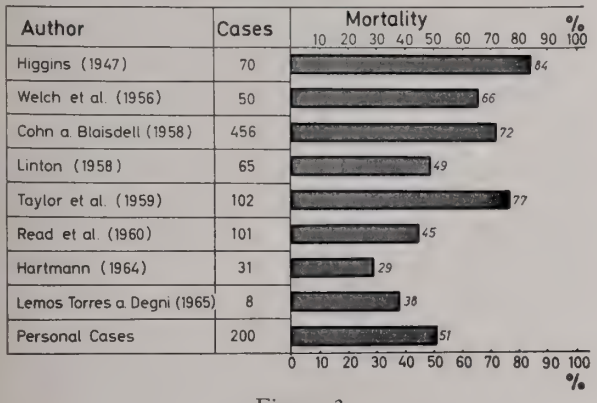


Figure 3

Treatment

The treatment of acute varicose vein bleeding is a very demanding task, and the decision for immediate operative intervention or for a conservative trial must be individualized. We have operated on 72 patients with varicose vein bleeding selected from 200 patients with this disorder (Figure 4). The best permanent results are obtained with portacaval anastomoses; however, the mortality with such a procedure is still quite high (Figure 5). The last 13 emergency shunt operations were successful in 11 cases (85%).

Our experience with 252 patients suffering from acute varicose vein bleeding has led us to establish the following therapeutic guidelines.

Prompt Replacement of Blood Loss

Any kind of varicose vein bleeding demands a prompt volume replacement, if at all possible, with blood. The damaged liver is quite sensitive to hypoxia.

Emergency Surgical Treatment of Cases with Acute Bleeding Oesophageal Varices

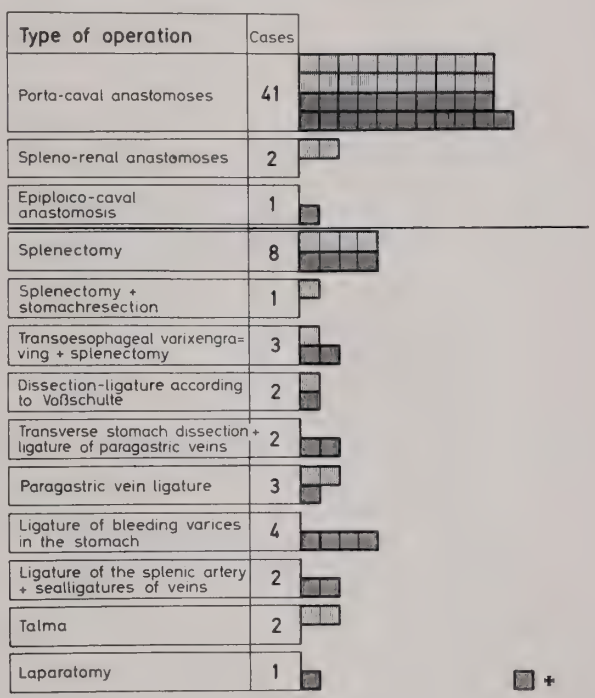


Figure 4

Portacaval Anastomosis as Emergency Operation

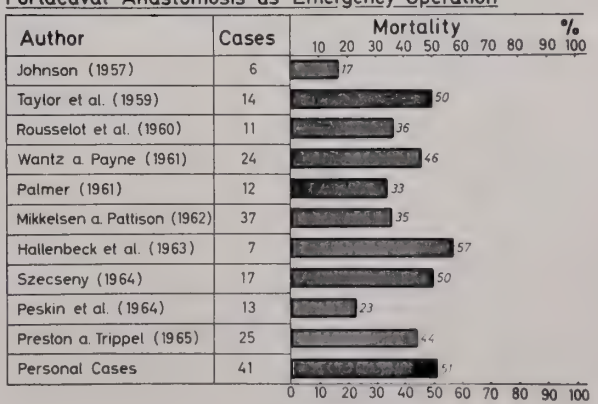


Figure 5

Conservative Management

Tamponage of the varices with a double balloon tube, as a rule, stops varix bleeding immediately. Important is early administration of laxatives and enemas in order to evacuate blood from the gut. Oral administration of antibiotics active against coliform bacilli (for example 2 to 5 grams neomycin within a 24-hour period) and conventional liver therapy are part of the medical regime.

Shunt Operation

In cases of incipient hemorrhage, especially in first occurrence of hemorrhage, an immediate shunt operation is desirable. If the liver function is satisfactory and the blood loss has been replaced rapidly, a delay is not justified.

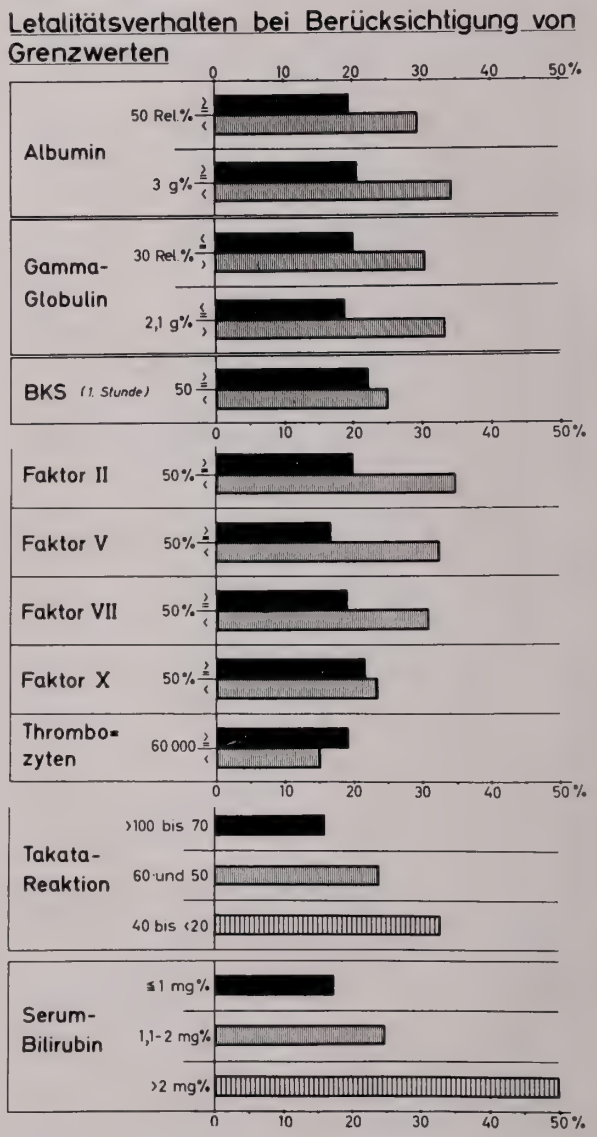
The operation should be carried out when the bowel has been cleared of blood, still with double balloon tube in place, about one or two days after onset of bleeding. In poor-risk cases we prefer the spleno-renal shunt.

A shunt procedure after the hemorrhage has ceased is the best measure to prevent recurrence of varicose vein bleeding. At present the portacaval anastomosis is virtually without competition as the most efficient modality for the treatment of hemorrhage and ascites.

The operative success of a shunt operation depends on the proper selection of patients. Ascites is a severe complication of portal hypertension; it is a sign of decompensation and must be eliminated before elective surgery is performed. Other important preconditions for a successful shunt operation are good general condition, a sufficient cardiac and circulatory function and a generally adaptable organism: to wit, the patient should not be too old. The choice of operative procedure and the indication for operation are determined by the anatomy of the portal system as demonstrated in splenoportography. The status of the liver functions, too, determines the indications and choice of procedure, and it is important to know that the liver function is satisfactory as evidenced by: (a) bilirubin under 2 mg %; (b) takata reaction above 40 mg %; (c) albumin above 3 gr %; (d) gamma-globulin below 30 rel. %; (e) coagulation factors II, V, VII above 50%; and (f) cholinesterase above 1600 mU.

Palliative Operations

If shunt operations are impossible and conservative treatment fails or if the hemorrhage recurs after removal of the double balloon tube, operative hemostasis at the point of hemorrhage may be tried. However, this is indicated only if liver functions have not deteriorated markedly as evidenced by incipient or manifest hepatic coma. When hepatic coma is present all methods of therapy fail, as a rule; any operation at this stage hastens the demise of the patient.



Translated: Mortality Patterns as Pertains to Borderline Tests.

Figure 6

Diuretics

In the days of surgical pioneering, ascites was the main indication for shunt operations; but the development of powerful diuretics, especially of the salt diuretics and of the aldosterone antagonists, has made it possible to control ascites due to liver cirrhosis by conservative means. We have treated 150 patients with liver cirrhosis and ascites without performing any portacaval anastomosis. Two patients were resistant to this therapy; one had a primary hepatocellular carcinoma and the other was a 65-year-old woman with abdominal carcinomatosis due to a primary breast cancer.

Mortality

Figure 6 shows the mortality in portacaval anastomosis in 225 patients in relation to some preoperative liver function tests. This includes 40 emergency operations which carried a mortality of 50%.

We have found needle- or open-liver biopsies unreliable as criteria for the operative procedure; these morphologic findings reflect only the status of one small portion of the liver. In cirrhosis especially one often finds varying degrees of inflammation and necrosis in different areas of the liver. However, if a small liver is found on the splenoportogram one may assume that only a small volume of

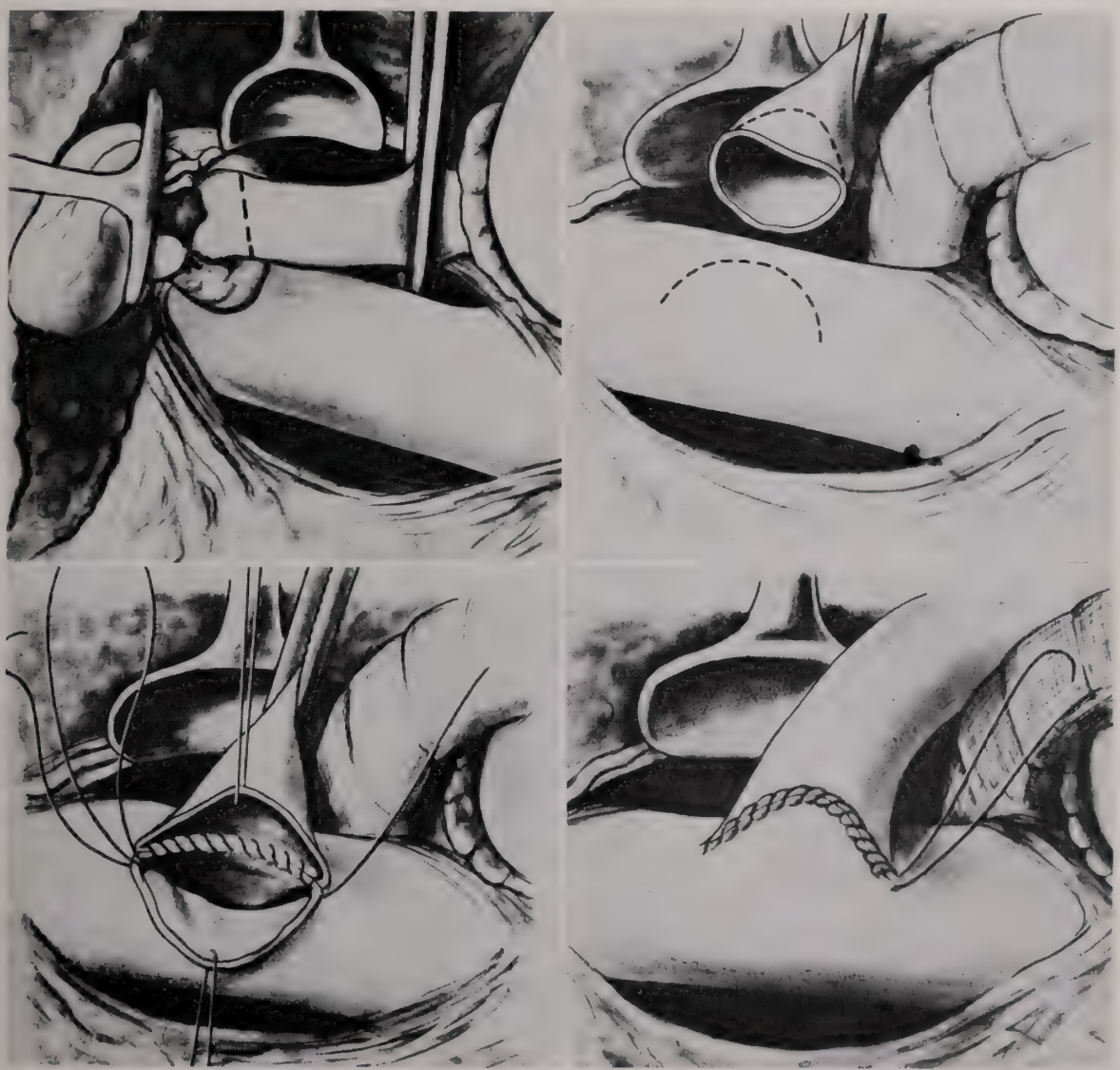


Fig. 7 (a-top left, b-top right, c-bottom left, d-bottom right)—Technique of termino-lateral portacaval anastomosis with flap formation.

liver cells is present, indicative of a small compensatory potential unable to handle the abrupt circulatory changes induced by a portacaval anastomosis.

Surgical Treatment

Portacaval Anastomosis

Two hundred eighty-four direct portacaval anastomoses were performed prior to March 15, 1968. Fifty-six were side-to-side and 228 end-to-side anastomoses. Fifty shunts were performed as an emergency for acute hemorrhage from varices—with a mortality of 48% (24 cases). The operative mortality, including the first 28 postoperative days, in 234 elective operations was 14.5% (34 cases).

The incidence of recurrent hemorrhages has been lowered by the use of a special technique for widening of the portal vein anastomosis (Figures 7a-d and 8a-d). Early recurrent hemorrhage occurred in 16 patients after portacaval anastomoses (5.6%), most of them from persistent varices after emergency operations (Table). Late hemorrhages occurred in five cases (1.8%).

Spleno-renal Anastomosis

Spleno-renal anastomoses are performed in patients with thrombosis of the portal vein and with a patent splenic vein available down to its junction with the superior mesenteric vein. During recent years we have also performed this operation in patients whose laboratory values indicated an increased risk for a direct portacaval shunt. If the spleno-renal anastomosis is wide enough it sufficiently decompresses the portal system and the varicose veins of the esophagus and stomach. The deprivation of the liver's venous blood supply is considerably less than in completely interrupting the portal vein blood flow to the liver. Our technique of spleno-renal anastomosis corresponds with our technique of portacaval anastomosis. The anastomosis should be made as far centrally between the splenic vein and the renal vein as possible. We have performed 35 spleno-renal anastomoses up to March 15, 1968, ten of them for a prehepatic obstruction and 25 for liver cirrhosis. The mortality in patients with cirrhosis and spleno-renal shunt, if done during the interval, was 8.3% (24 patients, two deaths). We lost one patient with a spleno-renal anastomosis performed for prehepatic obstruction. This was a 4½-year-old girl—the first shunt operation in our hospital.

Spleno-renal anastomosis should be performed as an emergency operation in bleeding varicose veins due to liver cirrhosis, if the risk for direct portacaval shunt is too high.

In our experience recurrent hemorrhage after a spleno-renal anastomosis is no more frequent than after a direct portacaval anastomosis. There was recurrent hemorrhage in two patients after elective surgery among 24 patients with liver cirrhosis (8.3%). Nine patients operated upon for prehepatic block and hemorrhage had no recurrent hemorrhage. Only the 4½-year-old child mentioned above suffered recurrent hemorrhage.

Coronaria-Caval Anastomosis

When the great coronary vein is widely patent we perform a coronaria-caval anastomosis for the lowering of the elevated portal vein pressure. We have done this in eight cases. For this we use the shortest route of vascular connection through the foramen of Winslow. This operation makes good sense as long as the width of the coronary vein

TABLE

Postoperative Varicose Vein Bleeding in 284 Direct Portacaval Anastomoses

	Early Hemorrhage	Death	Late Hemorrhage	Death
With intact anastomoses	7	7	2	2
Rethrombosis of portal vein after thrombectomy	7	7	2*	—
Thrombosis of normal-appearing portal vein	2	2	1	1

*Both cases are free of recurrence after spleno-renal anastomoses.

equals at least that of the portal vein. This anastomosis has been performed in six patients with liver cirrhosis and two with prehepatic block. There were no deaths and no recurrence of bleeding.

Mesenterico-Caval Anastomosis

A mesenterico-caval anastomosis was done in three patients. An omphalico-caval and an epiploico-caval anastomosis were done in one patient each. The latter thrombosed very fast.

During the shunt operation special attention should be paid to the possibility of stomach ulcers and gallstone disease. In 5% of our patients with liver cirrhosis we found gastric ulcers. Furthermore, we know of three cases who bled to death from gastric or duodenal ulcers several years after an apparently successful portacaval anastomosis. One patient died two years after the shunt operation from undiagnosed choledocholithiasis. Therefore, for the past ten years we have removed the gallbladder, if it contains stones, at the time of the shunt operation. In one female patient we performed at the same time a common bile duct exploration and a papillolithotomy.

Portacaval anastomoses, whether of the di-

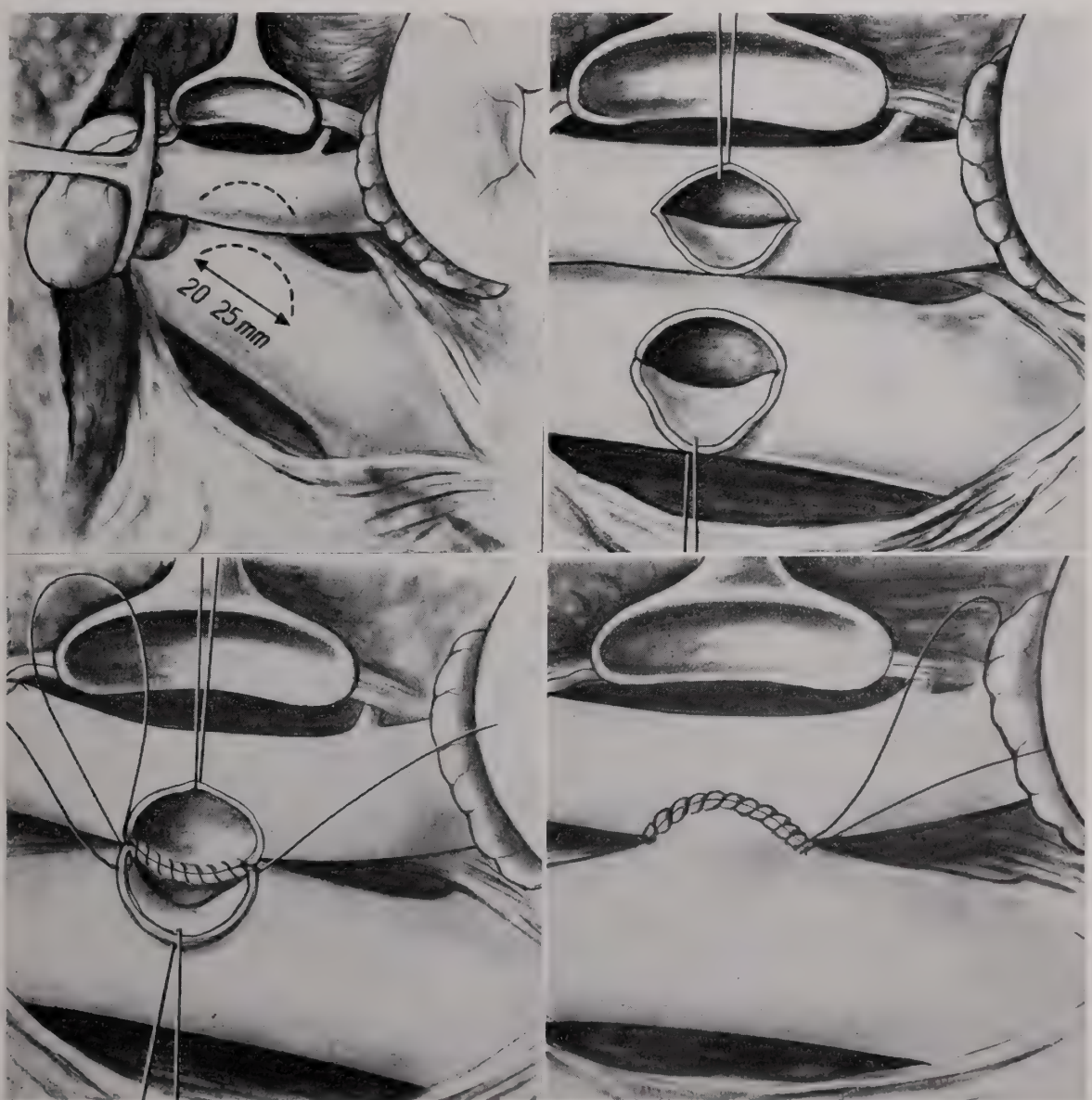


Fig. 8 (a-top left, b-top right, c-bottom left, d-bottom right)—Technique of latero-lateral portacaval anastomosis with flap formation.

rect or indirect type, insure freedom from recurrent hemorrhage. The operative risk is low when the proper indications are observed, and the proper operative technique insures freedom from recurrence. Acute varicose vein bleeding and cases where the operative indication is not clear-cut pose particular problems.

Encephalopathy

Portacaval anastomosis could well be considered the ideal method of treatment for complications of portal hypertension in liver cirrhosis were it not for the occasional occurrence of encephalopathy. Long-term observations have shown us that a portacaval anastomosis does not cause any additional liver damage. We have performed electroencephalographic and psychoanalytic examinations in cooperation with Dr. Penin (Department of Neurology, University Hospitals, Director Professor Dr. H. J. Weitbrecht) in more than 300 patients with liver cirrhosis and portal hypertension. The incidence of encephalopathy from hepatoportal origin and the speed of its development in non-operated patients (142 cases) and operated patients (114 cases) were equal. The degree of seriousness was also equally distributed; however, there were more acute forms in the group of patients who had undergone shunt operations, while the non-operated group contained more chronic forms. During an eight-year observation period of patients with portacaval anastomoses, the personality pattern of one third of the patients was without significance: one third had undergone no change after the operation, and one third had worsened during the period of observation. The psychic improvement of one third of the patients with portacaval anastomosis and cirrhosis came as a surprise.

Liver Function or Encephalopathy

There was a clear correlation between the degree of encephalopathy, as evidenced by psychopathological and electroencephalographic findings, and the liver function tests: the greater the depression of liver function, the higher the rate of encephalopathy.

At the present time it is still impossible to predict which patient will show personality changes after a portacaval anastomosis. There is little doubt that patients with markedly depressed liver functions are the most likely candidates. Cirrhotics with encephalopathy should not be subjected to a shunt operation.

Prophylactic Shunt

We perform prophylactic shunt operations only with great reluctance. This is based on the facts that only 60 percent of patients with varicose veins bleed, that the operative mortality is still high, and that there is always the threat of an acute postoperative encephalopathy. Our criteria for a prophylactic portacaval anastomosis are: (1) good general condition; (2) good liver function; and (3) pronounced esophageal varices in the absence of a caudally directed collateral circulation, as shown in serial splenoportograms.

Summary

Portacaval anastomosis has been a very useful operation in the treatment of life-threatening varicose vein bleeding due to portal hypertension in liver cirrhosis. The favorable early and late results should not deter us from seeking better operative procedures or conservative measures for the elimination of the danger of hemorrhage. With a proper patient selection the mortality is relatively low. Emergency operations in acute varicose vein bleeding, however, show a high operative mortality; but even in those circumstances the portacaval anastomosis, if done in time, is still the most effective treatment.

In cases with borderline liver function, a spleno-renal anatomosis is the procedure of choice.

A portacaval anastomosis does not cause additional permanent liver damage. Postoperative encephalopathy does not occur more frequently or more severely than in patients with varicose veins without a shunt operation. However, shunt operations cause more acute encephalopathies.

Ascites, once an indication for shunt operation, has become the domain of medical therapy. One should hope that further search for causes of portal hypertension may yield some specific drugs for an efficient lowering of the

portal hypertension. The portacaval anastomosis, even if it mimicks nature's efforts of collateralization, is still an unphysiological measure. It is therapeutically effective and tolerated to some extent by the organism, but it has its risks and is directed against only one complication rather than against the basic disease. Thus the whole problem still calls for a better solution.

Translated by: H. W. Heupel, M.D., Ph.D.

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Shakespeare: Medicine
Miscellaneous

Assimilation— "Note me this, good friend;
Your most grave belly was deliberate,
Not rash like his accusers, and thus answer'd:
'True is it, my incorporate friends,' quoth he,
'That I receive the general food at first,
Which you do live upon; and fit it is,
Because I am the store-house and the shop
Of the whole body: but, if you do remember,
I send it through the rivers of your blood,
Even to the court, the heart, to the seat o' the brain;
And, through the cranks and offices of man,
The strongest nerves and small inferior veins
From me receive that natural competency
Whereby they live.' "
"Ay, sir; well, well."
" 'Though all at once cannot
See what I do deliver out to each,
Yet I can make my audit up, that all
From me do back receive the flour of all,
And leave me but the bran.' "

—Menenius to Citizen in Coriolanus I, 1.

Great things can be reduced to small things, and small things can be reduced to nothing.—Chinese Proverb

Nobel Prize Winners in Medicine and Physiology

Camillo Golgi 1906

Santiago Ramon Y Cajal 1906

In recognition of their work on the structure of the nervous system.

"I have found two quite different kinds of nerve-endings in the tendons:

"(a) The one is represented by peculiar bodies which are quite characteristic in appearance, form, structure, and type of connection with the nerve fibrils, and are unlike any other in the known nervous end-apparatus of our organism; it is very probable, then, that their significance lies in correspondence with the function which muscles and tendons have to perform in common.

"(b) The other type is represented by bodies which likewise have a peculiar and striking appearance, but which, on the whole, find their counterparts in other known nervous end-organs of our bodies, which they resemble not only in anatomical structure but probably in function also.

"The principal anatomical characteristics of the musculo-tendinous organs can be summed up briefly as follows:

"In general they are spindle-shaped, and one of their ends is always connected with the fasciculi of the muscle fibers.

"Their size varies within fairly wide limits, from 70-80 microns in breadth and 300-400 microns in length to 100-120 microns in breadth and over 800 microns in length.

"Their outline tends to be very distinct and even appears at times in the form of a slender, glittering border, along which one catches sight of nuclei."

Besides his work in neuroanatomy, particularly his discovery of the neurons (Golgi cells), Golgi is distinguished for his later research in neuropathology.

"From the sum of my researches springs a general concept which comprehends the following propositions:

"The nerve cells are morphologic units, the neurons. . . . The morphologic dispositions attest that the nerve elements have reciprocal relations of *contiguity* and not of *continuity*.

"These facts involve three physiological postulates:

"(1) Since nature, in order to assure and amplify contacts, has created complicated systems of ramifications around the cells, it is necessary to admit that the nervous currents are transmitted from one element to another by virtue of a sort of induction, or influence at a distance.

"(2) It is also necessary to suppose that the cellular bodies and the dendritic prolongations are induction apparatus, since they represent intermediate links between the afferent nerve fibers and the axons.

"(3) Examination of the transmission of nerve impulses in the sense organs shows that the movement of the nerve impulse is *toward the cell body*, whereas in the axons it is *away from the cell body*."

The abridged quotation above summarizes Cajal's investigations complementing Golgi's discoveries. Cajal's research, in turn, became the point of departure for the work of Charles Sherrington and Egas Moniz.*

*With acknowledgements to Theodore Sourkes: Nobel Prize Winners in Medicine and Physiology, 1966.

Problems and Operative Technique in Portacaval Anastomoses

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PORTACAVAL ANASTOMOSES in patients with liver cirrhosis and portal hypertension have been used for 23 years for the treatment of bleeding varices from the upper digestive tract. The operation has been performed only in certain centers of different countries and continents. This geographic concentration has enhanced the systematic exploration of the pre- and postoperative pathophysiology. Long-term observations have made it possible to establish definite indications for shunt operations.

This communication is based on an operative experience with 360 patients who underwent direct or indirect portacaval anastomoses. The first shunt operation in Bonn, Germany was performed 15 years ago by Gütgemann. Since then surgery of the portal vein has, under his direction, developed into a special field of interest and research.

Some technical improvements which we introduced have proved of value and are worth reporting.

Selection of Patients

Criteria for patient selection with portal hypertension are the general and circulatory condition, the age of the patient, and the liver function (Table 1). A preoperative percutane-

TABLE 1

Criteria in the Selection of Patients with Liver Cirrhosis for Portacaval Anastomoses

1.	Good general condition	
2.	Good circulatory status	
3.	Portal vein free of thrombi	
4.	Adequate liver size (on splenoportogram)	
5.	Bilirubin	under 2 mg%
6.	Takata	above 40 mg%
7.	Serum albumin	above 3 gr%
8.	Cholinesterase	above 1600 mμ
9.	Prothrombin	above 50 %
10.	Factor V	above 50 %
11.	Factor VII	above 50 %

*From the Surgical Clinics and Poli-Clinics; University of Bonn. Director: Professor A. Gütgemann, M.D.

ous splenoportogram determines the operative method. As a rule, patients with several bleeding episodes from varices of the esophagus or the stomach are selected for operation. The prophylactic shunt operations require stringent criteria with regard to liver function. They should be reserved for cases with a definite bleeding tendency and marked esophageal varices, as demonstrated in splenoportogram, and predominantly cranial collateral circulation.

Preparation of Patient

The preoperative preparation of patients with liver cirrhosis and portal hypertension who have adequate liver function is the same as that for other patients with routine operations. Cirrhotics with liver decompensation require long-term medical therapy.

The anesthetic of choice used to be Halothane. We discontinued its use when we saw several cases of early postoperative coma after the use of this anesthetic, even though it is impossible to definitely implicate Halothane. We are now using neuroleptanalgesia* in patients with liver cirrhosis with excellent results. The patients awaken rapidly after the operation, regain their activity soon, and can leave their bed on the day after operation, able to eat or at least to drink.

The Operation

Incision

The operative approach for the portal vein is always satisfactory through a right subcostal incision which is extended laterally. Thoracoabdominal incisions are unnecessary. After mobilization of the duodenum, the hepatoduodenal ligament is elevated with a Rehn-spatula and the portal vein easily dissected on its lower border.

Operative Technique

The choice between an end-to-side or side-to-side anastomosis is optional and depends on the anatomical findings. Schreiber (1963) has proved that there is no difference between an end-to-side and side-to-side portacaval anastomosis with respect to blood flow and liver function. Thus it is unnecessary to insist on a side-to-side anastomosis between portal vein and inferior vena cava. The end-to-side anastomosis in most cases is technically easier and can be done faster. However, if anatomically feasible, we sometimes perform a side-to-side anastomosis.

Because we have seen several postoperative thromboses in the portal vein ramifications, when the transection was made at the bifurcation, which led to liver necrosis and death by coma, we now ligate the main branch of the portal vein far enough from the bifurcation to maintain a communication between the branches. Since we have started this practice we have not encountered early postoperative coma in operations which were done in the hemorrhage-free interval. The degree of postoperative leukocytosis has also definitely decreased with this practice. It may be assumed that there is a continuing circulation between the portal vein branches which prevents portal thrombosis in the liver branches.

Gütgemann has originated a very useful and successful anastomotic technique; by using his *flap formation* at the portacaval anastomosis

*See Test Your Word Score Page 1583.



Fig. 1—a (left), b (middle), c (right)—Schematic incision and suture of a termino-lateral portacaval anastomosis.



Fig. 2—a (top-left), b (top-right), c (bottom-left) and d (bottom-right)—Construction of a termino-lateral portacaval anastomosis.

it is possible to avoid anastomotic stenosis of the portal vein (Figures 1 and 2). The incidence of postoperative portal vein thrombosis cited in the literature is 4 to 20%. Using our operative technique we were able to lower it to 2%.

Anticoagulation

We have discontinued the use of *heparin* in portacaval anastomoses. When heparin was injected in high concentrations into the proximal portal vein segment after this was clamped off and before anastomosis was done, it appeared to damage the vein walls. Occasionally we have seen postoperative thrombosis of the anastomosed portal vein in the presence of a wide anastomosis, and we suspected a possible intimal reaction of the portal vein as a possible cause. After discontinuing heparin four years ago we have encountered no more postoperative thrombotic occlusion in portacaval anastomosis. Anticoagulation of the clamped proximal portal vein for the prevention of thrombosis during the anastomosis is unnecessary in our experience. There is increased fibrinolytic activity as a result of venous congestion. This makes it possible to interrupt the blood stream for up to 30 minutes without the danger of thrombus formation.

Complications

Ascitic flow through the drain site in the area of the portacaval anastomosis has been a nasty postoperative complication, presenting a real nursing problem. For days and weeks the patients were lying on wet pillows and had to be redressed up to 12 times a day. We suspected the cause to be the transection of distended retroperitoneal lymphatic vessels over the vena cava. We now *ligate the retroperitoneal tissue* during the dissection of the vena cava, thus eliminating this complication. At present we still drain for three to five days.

The *postoperative treatment* demands no particular measures. Our therapeutic regime is summarized in Table 2.

Translated by: H. W. Heupel, M.D., Ph.D.
References may be secured from the Author.

TABLE 2

Outline of Immediate Postoperative Management after Portacaval Anastomoses

1. After the wakening intravenous drip of 1500 ml until the next morning wih 50 meq potassium lactate.
2. Starting with the day of operation a daily liver cocktail with Laevulose, B-vitamins, adrenal cortical hormones and 5 million units penicillin for 10 days.
   To be injected: 1 gr vitamin C, 10 mg vitamin K_1
   By mouth: 200 mg Spironolactone for five days
   50 mg Spironolactone for five more days.
3. During the first three postoperative days fluid administration according to hematocrit value (base 40) by infusions with glucose, levulose, Ringer's solution. Potassium substitution.
4. Postoperative patients are permitted to drink on the first postoperative day and to have light meals if they desire. They are to walk around the bed from the first postoperative day on and are permitted to leave the room starting on the sixth postoperative day.

Comments and Conclusions

In view of the increased incidence of chronic parenchymal liver damage one may foresee a shortage of centers equipped for portal-vein surgery. Surgeons in other large institutions may be expected to add portacaval anastomosis to their operative repertoire, since the clinical and technical ground work has been done. In presenting special operative and technical aspects we hope to contribute to previously gained experience and to a reduction of operative failures. However, even more work is to be done in the search for new approaches to the alleviation of portal hypertension.

Years of investigation have led to a standardization in indication and operative technique of portacaval anastomosis for portal hypertension in liver cirrhosis. The neglect of small technical details can lead to failure. Some of these technical factors have been discussed. The operative technique has been briefly described, and a review of indications for operation and of postoperative management has been presented.

A cold is both positive and negative; sometimes the eyes have it and sometimes the nose.—William Lyon Phelps

Arterial Hypertension in Urologic Diseases

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IN THE PAST we have repeatedly pointed out the surprising frequency of arterial hypertension in patients with urologic defects, particularly in cases of unilateral renal involvement (Table).

Selection of Patients

Diastolic pressures above 90 mm/Hg at rest were considered the criterion for arterial hypertension. For sharper differentiation a further subdivision of 193 cases was isolated from the 1964 to June 1967 list: ninety-three cases with diastolic pressures from 90-100 mm/Hg and 100 cases with diastolic pressures exceeding 100 mm/Hg.

These figures may appear rather high; however, we must remember that we are dealing with a selected group of patients who were referred for urological therapy. Thus our study will not permit conclusions concerning the frequency of renal hypertension compared to other causes of high blood pressure.

We can differentiate two groups among these patients.

Urologic Problems

The first category consisted of patients who were referred to the clinic primarily for the purpose of urological investigation or therapy, and whose hypertension either had been no factor at the time of their admission or had constituted only a secondary aspect. Usually no treatment had been administered for hypertension. This group included nephroptoses, hydronephroses, renal cysts, urinary tract calculi and renal tumors.

Renal Hypertension Problems

Comprising the second category were patients referred to us primarily because of renal hypertension, in whom medical treatment had been unsuccessful. This group included hypoplastic kidneys, renal artery stenosis, inflam-

*From the Urologic Section of the Surgical University Clinic, Bonn. Director: Professor A. Gütgemann, M.D.

matory contracted kidneys or pyelonephritis due to calculi.

Diagnosis

In these 446 cases of urologic disease with associated arterial hypertension we made every reasonable effort by means of history, para-urologic history, cardiologic, neurologic and metabolic investigation to rule out other than urologic causes of hypertension.

The high incidence of hypertension is not surprising when one considers the studies of J. A. Wilbur of the Georgia State Health Department, where the consecutive examinations of 3,000 people of Baldwin County, State of Georgia (U.S.A.), found 630 hypertensive persons of whom only 55% knew of their condition. Three hundred and forty-seven remembered that previously a physician had made the diagnosis of hypertension but in most cases had discontinued their medication after three months.

Only 352 of the 630 hypertensive patients in Wilbur's series had consulted a physician in the previous three years. One hundred and seventy-six needed treatment when they were seen at the State Health Department. Wilbur also pointed out that hypertension accounts for 5% of all deaths directly and can be considered an important complication in 13% of patients with another disease. He concluded that in the subsequent five years the lives of one million Americans could be saved if therapy could bbe instituted. Thus roughly outlined is the manner in which every physician can contribute to the eradication of the problem.

TABLE

Unilateral renal diseases	1950 - 1963 Diastol pressure above 90 mm Hg	1964 - 1967 Diastol. pressure 90 - 100 mm Hg	1964 - 1967 Diastol. pressure above 100 mm Hg	Total number
Hypoplasia	8	2	4	14
Vascular abnormalities	25	1	6	32
Cysts	15	5	10	30
Hydronephrosis	38	7	16	61
Calculi in renal pelvis	36	23	20	79
Ureteral calculi	66	30	16	112
Contracted kidney	24	21	23	68
Tumors of kidney or renal pelvis	41	4	5	50
				446

Distribution and interrelation of varied underlying defects in 446 patients who were admitted in the period from 1950 to June 1967 with renal defects and accompanying arterial hypertension.

Routine Blood Pressure

By taking the blood pressure of every patient, no matter what his presenting complaint, we are convinced that a considerably greater number of hypertensive patients will be found than had been assumed to exist.

Urologically speaking, recognition of therapeutic peculiarities in hypertensive patients means that arterial hypertension must be strongly considered in the therapeutic measures. Not only the pathological-anatomical state of the affected organ has to be taken into consideration but also to what extent the chosen therapy might be effective for hypertension. Such considerations presume that routine urologic examination should be completed by additional studies as soon as paroxysmal or constant arterial hypertension is found.

Additional studies would include:

a. Early and late exposure during urography
b. Renal arterial angiograms
c. Angercamera-timed scintillation counter with programmed computer
d. Clearance studies
e. Howard's test, Rappoport test, and Stamey test
f. Angiotensin-infusion test (Kaplan)
g. Determination of renin-angiotensin as well as aldosterone assays
h. Electrolyte balance

Special consideration arises if hypertension is present together with urologic abnormalities but cannot be related to other causes.

Therapy

Renal Hypoplasia

Functional hypoplastic kidneys which do not produce symptoms, are free from chronic infection, and do not cause hypertension should be left alone. But as soon as hypertension develops, nephrectomy should be considered. The earlier this measure is instituted the more likely will hypertensive damage to the contralateral

kidney and secondary hypertension be prevented.

Arterial Defects

It is important to distinguish between intrarenal vascular changes and obstructions of the renal artery. In intrarenal angiomas, arteriovenous fistulas, renal infarcts due to emboli or thromboses, only partial resection of a kidney is needed. But defects of the renal artery without general destruction of renal parenchyma may be relieved by measures such as resection of the artery, arterial transplants, angioplasty, bypass or splenorenal anastomosis.

Although corrective vascular surgery, particularly the bypass, has not proven to be as satisfactory as had been assumed, it must be emphasized that an amelioration of arterial hypertension can be accomplished in many cases. Normotensive status can be reached in 50-60% of the cases; in another 10-20% a considerable improvement can be obtained.[1,10] Following is a typical case:

Case Report

Case 1

A 26-year-old male had stenosis of the right renal artery and poststenotic aneurysm with Recklinghausen's neurofibromatosis. His blood pressure, which was 210/120, was resistant to therapeutic measures. After resection of the stenosis and the aneurysm and end-to-end anastomosis to the aorta, the blood pressure dropped (Figure 1), followed by a secondary rise to preoperative values. However, after antihypertensive medication another drop occurred and the patient's blood pressure was permanently reduced.

*See Test Your Word Score, Page 1583.

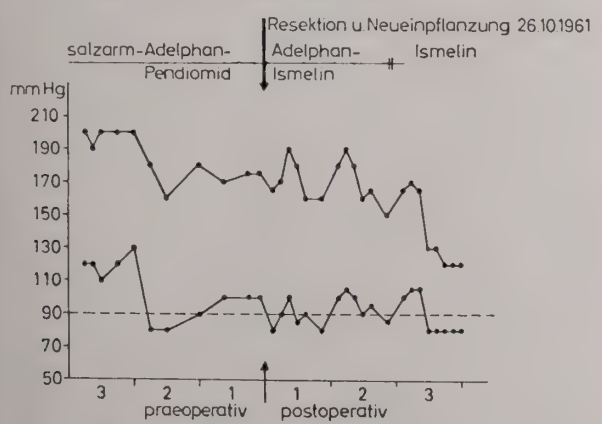


Fig. 1—26a Male (3002/61) Right renal artery stenosis. Preoperatively poor response to entire hypertensive therapy. Postoperative vacillations of blood pressure with final normalcy through administering ismelin.

Renal Cysts

With hereditary renal cysts as well as with unilateral polycystic kidneys the blood pressure is frequently elevated; in this series hypertension was found in 60% of cases. With the so-called polycystic kidneys, which by current concepts involve both organs, a diminution of the blood pressure may be expected only after surgical correction when one kidney is affected. The most valuable methods of surgical intervention are ignipuncture* to the small cysts or resection of the large as well as solitary cysts. Nephrectomy is contraindicated, since one may expect a cyst-predisposition even in the seemingly normal contralateral kidney. With conservative measures, which can result in amazing remissions and even with advanced loss of parenchyma, it has been possible to effect postoperative drops of blood pressure in practically all patients. It is difficult, of course, to differentiate the beneficial effect of surgery from the therapeutic value of treating the urinary tract infections usually found in these cases.

Hydronephrosis

Arterial hypertension was found in approximately 20% of 234 patients with hydronephrosis secondary to congenital ureteral stenosis. With the exception of far advanced destruction of renal parenchyma due to congenital hydronephrosis, where nephrectomy becomes mandatory, the therapy of choice is resection and plastic repair of the renal pelvis.[5,6,7,8] The indication to use this procedure may be quite liberally applied because of the kidney's regenerative ability. Following the establishment of normal urine excretion it may be expected that normal renal blood flow and decrease of the concomitant hypertension will occur. If the surgical repair fails to result in satisfactory renal function and relief of hypertension, a secondary nephrectomy may become necessary, after which one may observe final relief from hypertension.

Pyelonephritic Hypertension

In order to obtain benefit in a concomitant pyelonephritic hypertension it is mandatory to control the urinary pH by diet and medication, along with long-term antibiotic therapy and an

adequate "lavage of the urinary tract" by oral fluid intake as well as by instrumental irrigation in four-week intervals for the duration of one year. The following are cases in point:

Case 2

A 33-year-old male was admitted to the hospital with congenital left hydronephrosis. During two years prior to surgery progressive hypertension in spite of low Na-diet and at times antihypertensive medication. Plastic surgery of left renal pelvis on January 14, 1963. Routine postoperative care without antihypertensive therapy. A distinct reduction of hypertension ensued, although desirable diastolic pressures below 90 mm/Hg were not attained (Figure 2).

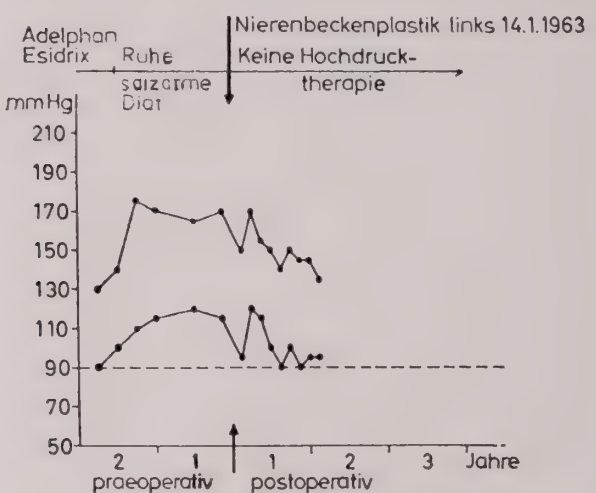


Fig. 2—33a Male (333/63) congenital mechanical hydro nephrosis on the left. Postoperative drop in blood pressure without antihypertensive medication. No return to completely normal.

Case 3

A 46-year-old female was admitted with congenital mechanical right hydronephrosis. During two years prior to surgery progressive arterial hypertension. Bedrest and low-Na diet lowered blood pressure even prior to surgery. Obvious drop in pressure after surgery to normal range for three years postoperatively. Then renewed if moderate hypertension, influenced favorably, however, by bedrest, low Na-diet and sedation (Figure 3).

Urinary Calculi of Ureters or Renal Pelvis

Arterial hypertension is associated relatively frequently with calculi of ureters and renal pelvis, particularly with complete obstruction of a ureter or calyx and complicating pyelonephritis. Sometimes there is an associated stenosis of the renal artery in cases of urinary tract calculi with concomitant hypertension, suggesting the need for an angiographic investigation wherever urinary tract calculi are associated with hypertension. The problem then arises whether, with removal of calculi, one should also correct vascular stenoses in order to have a favorable effect on hypertension and to prevent recurrence of calculi due to tissue anoxia. The following case demonstrates that it is possible to correct hypertension of long duration. Two years prior to admission this patient had been known to suffer from a ureteral calculus with complete ureteral obstruction and associated hypertension (Figure 4).

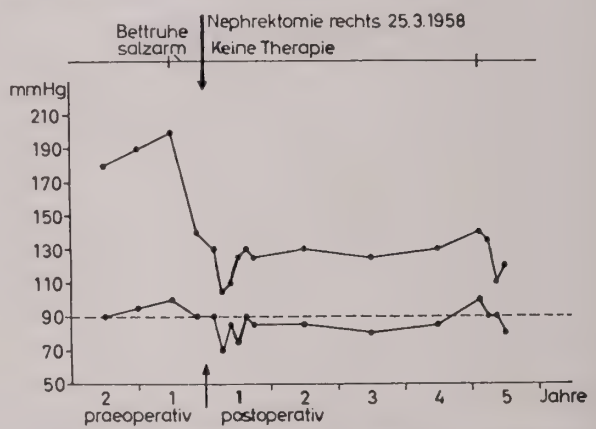


Fig. 3—46a Female (837/58) Congenital mechanical right hydronephrosis. Normal blood pressure after surgery. Recurrence after four years. Successful return to normal with antihypertensive therapy.



Fig. 4—Stenosis of the renal artery with calculus and pyelonephritis. Nephrectomy was done.

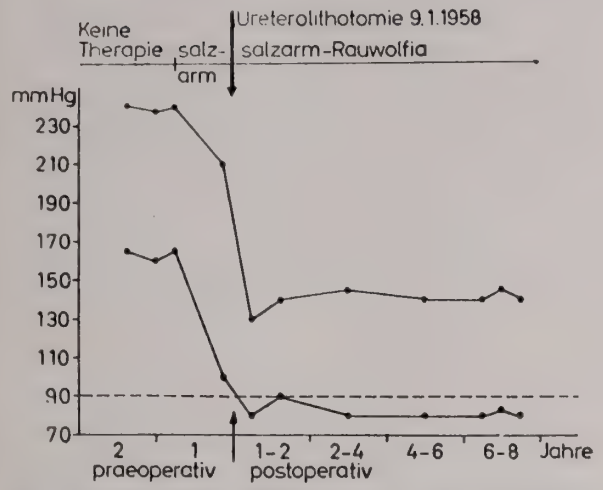


Fig. 5—54a Female (2957/57) Left ureteral calculus. Normal blood pressure after operation with antihypertensive therapy.

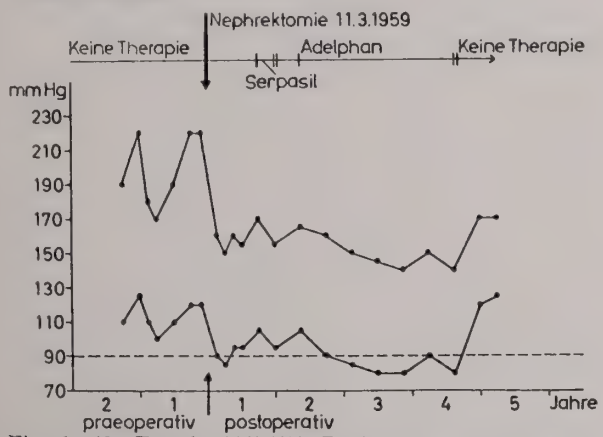


Fig. 6—43a Female (459/59) Pyelo-nephritic contracted kidney on the right, drop in the blood pressure after nephrectomy. Normal pressure with antihypertensive therapy. Resumed rise of blood pressure when therapy was omitted.

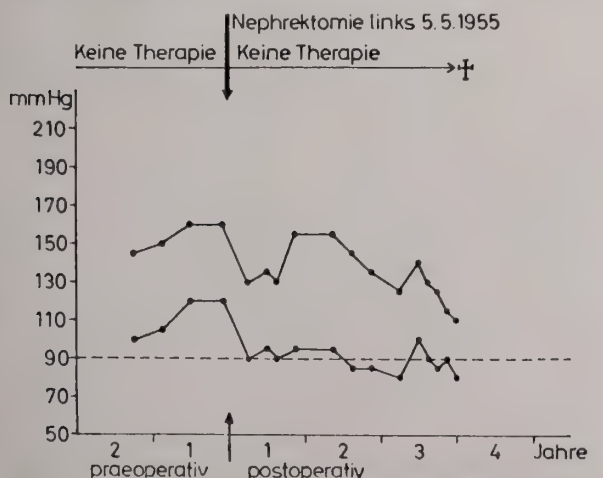


Fig. 7—54a Male (47/58). Left hypernephroma. Died of multiple metastases in 1960. Postoperative drop of blood pressure. Without antihypertensive therapy there occurred a rise in the third year after surgery. Another drop of blood pressure with tumor petechia.

Case 4

A 54-year-old female, occluding left ureteral calculus. Hypertension for two years prior to surgery. Low Na-diet and bedrest had resulted in only moderate improvement. Blood pressure became normal however, after ureterolithotomy, subsequent low Na-diet and Rauwolfia therapy (Figure 5).

Contracted Kidneys

In contracted kidneys, due to inflammation or calculi followed by inflammation, nephrectomy is the only reasonable solution and usually leads to normotensive states if hypertension has not been present for too long a time (Figure 6).

Patients with contracted kidneys have a better prognosis concerning postoperative blood pressure than those with other renal diseases, as stated previously by Braasch, Pickering and Heptinstall, Thompson, Gifford and von Niederhäusern and Wildbolz.

Tumors of Kidneys and Renal Pelvis

We also observed arterial hypertension in tumors of the kidney and renal pelvis, where nephrectomy is indicated on principle. Forty-one (17.4%) of 247 such cases had associated hypertension. Nephrectomy may be regarded as curative therapy for this type of hypertension, considering that 16 of the 22 patients who were followed after surgery showed a material drop in blood pressure (Figure 7).

Although in these cases the survival of patients is determined by the course of the malignancy, a curtailment of life expectancy due to hypertension can be avoided; but such a shortened survival may occur and lead to death if the tumor is treated solely by irradiation.

Prognosis

Extensive follow-ups on our patients showed that one can expect a fall in blood pressure in 30 to 60% of the cases. On the other hand, one may also anticipate renewed rise of blood pressure within two years following surgery in 25 to 30%. This appears to be the case particularly in hypertension of long duration in which the postoperative blood pressure is not observed closely and rising pressures are not treated promptly by antihypertensive therapy. The well-planned, long-term antibiotic therapy of an existing urinary tract infection is equally

important in order to avoid postoperative rise of blood pressure. In the case of renovascular hypertension immediate antihypertensive postoperative treatment is mandatory. It is significant that hypertension which was resistant to therapy before operation will respond to such therapy postoperatively.[3,8,9]

Based on our recent experiences there is assurance that the prognosis of renal hypertension can be further improved, if therapy is not limited to surgery alone but includes postoperative controls and, if necessary, long-term antihypertensive and antibiotic treatment. Leishman's findings indicate the importance of a lowered blood pressure, even if only moderate. He found that decline of the diastolic pressure by 10 to 30 mm/Hg increased the survival time of hypertensive patients from 1/6 to 1/3.

Translated by: Horace A. Zinneman, M.D.

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Interpretive Fallibility

Of recent years the powers that be in the profession have made it quite impossible for one to take a firm stand in an opinion unless backed by a blood chemistry analysis, cardiograph, gastrointestinal barium meal and enema, fluoroscopy, gastric content examination, and needling. These are invaluable gadgets to eliminate doubt or settle argument, but used indiscriminately and as a matter of routine they destroy faith in one's ability to reach a satisfactory conclusion. . . . And the interpretation of graphs, X rays, and charts is still subject to the frailty of human inaccuracy and indecision.

I have watched genitourinary specialists operate for a kidney stone to find that the shadow on the X-ray plate was a gallstone. I have been in consultation with heart specialists whose findings indicated coronary occlusions, when in reality the gall bladder was the seat of the disease, and not the heart. I have heard radiologists claim the presence of an ulcer of the stomach when an operation revealed its absence. I operated upon a subphrenic abscess demonstrated by an X-ray expert and found nothing. I was almost persuaded once by an eminent pathologist to remove a young female's entire generative organs for cancer when none existed, because of the microscopical findings; the woman still lives fifteen years later, without mutilation. I have seen normal gall bladders explored because the interpretation of the pictures was misunderstood. I could go on indefinitely reciting proofs that the machines are not foolproof.*

*Joseph A. Jerger, M.D.: Doctor—Here's Your Hat, 1939.

Appendix

The modern king has become a vermiform appendix: useless when quiet; when obtrusive, in danger of removal.—Austin O'Malley

Preservation of Kidney and Liver Transplants

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THE PRESENT TECHNIQUE of organ preservation extends the ischemia tolerance time to several hours. This time interval, however, does not allow for transportation of the organ to the transplantation center, mobilization of the surgical team, preparation of the recipient, and performance of histocompatibility tests. It is thus urgently necessary to develop methods of prolonged organ preservation and to establish an organ bank, similar to a blood bank, in which organs are available at any time.

Preservation Principles

Hypothermia

Hypothermia reduces metabolic activity, lowers oxygen requirements, and decreases metabolic waste products. The O_2 consumption of the tissues diminishes exponentially‡ with falling temperatures, thus prolonging the ischemia tolerance. Hypothermia can be employed in different ways:

1. Cooling to temperatures slightly above 0°C.
2. Cooling below 0°C. without freezing
3. Freezing

While cooling below 0°C. reduces metabolism markedly and freezing results in a virtually complete cessation of metabolism, the usefulness of cooling to 2-4°C. is restricted to only a few hours.

Hyperbaric Oxygenation

High pressure intensifies molecular motion. Diffusion of oxygen into the tissue and of carbon dioxide out of the tissue is accelerated by high pressure. Because the number of diffusible particles is proportional to the partial gas pressure, employment of pure oxygen increases the effect of this procedure, depending on the organ thickness and the pressure applied. Because of an organ-specific sensitivity

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‡See Test Your Word Score, Page 1583.

to hyperbaric oxygenation, however, there is a practical limit for the use of high oxygen pressures.

Metabolic Inhibition

The drug-induced reversible enzyme-inhibition resulting in a reduced metabolism is a distinct aid in organ preservation; it prolongs the ischemia tolerance considerably. Phenothiazines, for example, inhibit enzymes[56]. Perfusion with reversible metabolic inhibitors, such as magnesium-sulfate, Adenochrome or sodium fluoride results in prolonged survival of various organs up to six hours[43]; but this method has advantages over simple hypothermia only in combination with other methods of organ preservation.

Continuous Perfusion

Organ perfusion by means of a pump-oxygenator has gained importance. Ideally it produces a continuous blood circulation in the organ, providing for a steady and adequate elimination of carbon dioxide and metabolic waste products as well as for a continuous supply of oxygen and energy. The most important precondition for a successful procedure, besides the oxygenator and pump, is a satisfactory perfusate. The efficiency of this method is limited, however, because of our inability to reproduce the physiological conditions exactly and completely.

Hypothermic perfusion permits the use of erythrocyte-poor or -free fluids, thus reducing or eliminating damage or destruction of erythrocytes by the pump. Perfusion pressures, which can produce severe organ damage even at so-called normal levels may be decreased[2,98]. In hypothermia using a pressure of 10 mm. Hg., an organ perfusion with 2-4 ml/minute and with a perfusate of 50% blood and 50% balanced, buffered electrolyte solution and low molecular weight dextran, or with albumin and heparin, results in a good organ conservation for up to 48 hours[2,98].

The effectiveness of a preservation method can be best ascertained by function tests after the transplantation, when irreversible ischemic damage and secondary circulatory damage is to be excluded. Function tests during the preservation are informative only when the employed technique—as in hypothermia—does not result in a reduction of the metabolism. The vitality of an organ may be evaluated by determining its adenosine triphosphate-reserve, the metabolic products of anaerobic glycolysis and the activity of various enzyme systems[9,46]. Important morphologic changes can be detected through electron microscopic and histologic studies in all phases of conservation[103,111,112]. A relatively reliable criterion is the avoidance of weight gain of the organ and maintenance of a stable pH-value.

The Kidney

The ischemia tolerance of the normothermic human kidney is quoted as varying between 90 and 120 minutes. After 60 minutes an impaired kidney function appears; 90 minutes of ischemia result in severe tubular damage, and after 120 minutes the damage becomes irreversible. The following methods of kidney preservation have gained practical importance:

Normothermic perfusion

a. By gravity
b. By oxygenator-pump-system

In contrast to kidney perfusion with an oxygenator-pump-system the normothermic gravity perfusion has gained little importance. The perfusion apparatus and the composition of the perfusate are designed to create physiological conditions, providing adequate circulation, oxygenation and nutrition of the kidney graft. Blood is the preferred perfusate since the oxygen capacity of red-cell-free solutions is inadequate at normal temperatures. Diluted blood is hemodynamically superior to undiluted blood. Telander recommends 200 ml. of fresh heparinized blood to which 100 ml. physiologic electrolyte solution and 50 ml. low molecular dextran are added. The urine output must be balanced by continuous replacement with electrolyte solutions. By combining perfusion dialysis and perfusion, the ischemia tolerance can be prolonged[43,85].

Figure 1 shows Paquet's apparatus consisting of an organ container, oxygenator and pump. Others have described modifications[7,8,18,21,37,38,43,85,87,94,95]. Pig kidneys perfused with pulsatile flow survived about 12 hours[67,68,72]. The urine output was 4 ml/minute at blood

flows of 150-300 ml/minute. A better and longer continuation of kidney function was obtained only by maintaining pulsatile flow rather than non-pulsatile perfusion[68,72]. Telander maintained sheep and baboon kidneys in a functional state up to 24 hours; but only those kidneys that were grafted within seven hours after harvesting resumed function[94,95]. The advantage of this perfusion procedure is physiological preservation; its disadvantage is the large apparatus required. At times an uncontrollable rise of pressure occurs in the perfusion system, resulting in vascular damage and extravasation followed by decreased kidney perfusion and oliguria[39,69,70,103,112].

Hypothermia

a. Osmodiuresis—preservation-hypothermia

b. Combination of gravity-perfusion and hypothermic osmodiuresis

c. Combination of gravity-perfusion hypothermia osmodiuresis, and hyperbaric oxygenation

d. Perfusion hypothermia (gravity, low-flow, mechanical)

e. Combination low-flow-perfusion, hypothermia and hyperbaric oxygenation

Many experimental investigations have shown the protective mechanism of hypothermia against ischemic kidney damage;[3,4,11,16,18,20,21,29,44,64,78,79,80,83,84,93,96,97,100,101,105,110,114] its clinical value has been demonstrated in many human kidney transplantations[5,13,16,22,32,45,59,88,89,92]. It has been demonstrated on the dog kidney that there is a logarithmic relationship between temperature and oxygen consumption; the O_2-consumption of 100 gm. kidney at zero° C. is reduced to 0.075 ml/minute[52].

The cooling of kidneys to 2°-4° centigrade combined with other preservation methods has proven superior experimentally and clinically[2,55,98]. Therefore we shall omit mention of the many experiments with hypothermia combined with the use of antifreeze substances and with freezing alone[15,17,24,75,77,83,84].

In the *osmodiuresis-hypothermia method* of

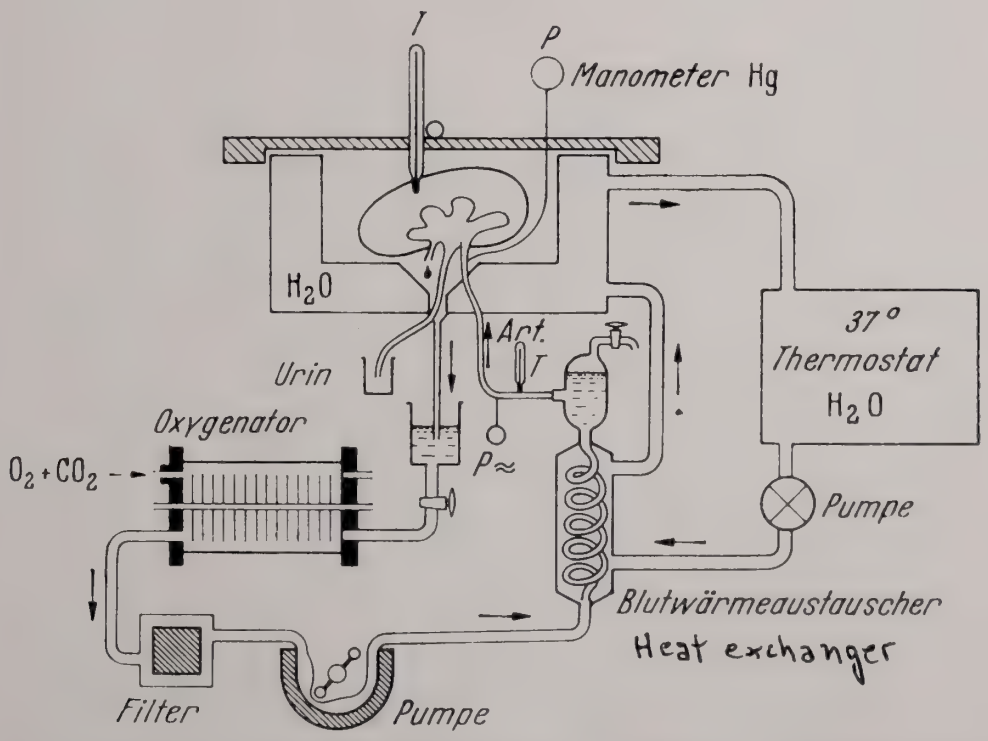


Fig. 1—Perfusion system for isolated kidneys (after K. J. Paquet et al., Langanbeck's Arch Klin Chir 304:735, 1963.

organ preservation the donor receives 250 ml. of a 20% mannitol solution* intravenously prior to nephrectomy. The excised kidney after drainage of blood is placed in a plastic bag. It is then cooled and stored in a thermo-apparatus (Figure 2) charged with a coolant. During the vascular anastomosis and after releasing the circulation to the transplant the recipient receives also 250 ml. of a 20% mannitol solution[101,104]. With the use of this method for periods of up to six hours Vahlensieck et al. observed in patients an immediate postoperative resumption of function[101,104].

Histologic and particularly histometric investigations[103,112] led us to use the combination of hypothermic osmodiuresis with an initial hypothermic gravity perfusion of five to 10 minutes. We have found a solution† developed by Largiader most suitable:

A.

Basic Solution

Sodium	140 mEq/liter
Potassium	7 " /liter
Calcium	5 " /liter
Magnesium	3 " /liter
Chlorine	105 " /liter
Lactate	50 " /liter
Glucose	2.0 gm/liter
Albumin	12.0 " /liter
Mannitol	0.5 " /liter

B.

Supplementary Solution

Tris buffer 0.3 molar	1.25 ml.
Sodium bicarbonate	4.8 mEq.
Procain hydrochloride	0.5 gm.

pH 7.25 to 7.38 at 6°C.; osmolarity 320 mos/ml.; 50 mg/liter of heparin (pH 5.5) are added and the pH is adjusted to the value listed

*Osmofundin, Braun, McLspurgan.
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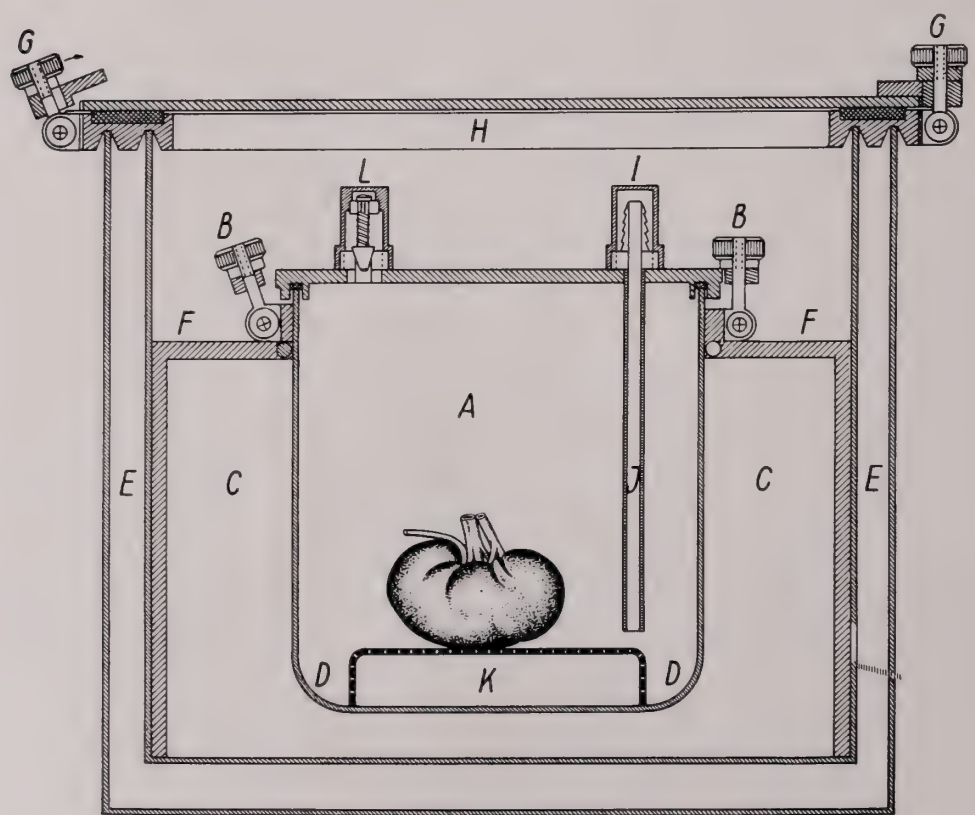


Fig. 2—Container for transplant preservation under hypothermia and with hyperbaric oxygenation (after W. Vahlensieck: Vhdl Dtsch Ges Urol, 1965. Springer-Verlag, Berlin-Gottingen-Heidelberg, 1966.)

above. The addition of other medications such as Complamin*, Euphyllin†, Intensain‡, Papavarin hydrochloride or Persantin§ serves to protect the organ additionally[23,39,62,67,69,70,72,109].

Simultaneous hyperbaric oxygenation and hypothermia prolong the ischemia tolerance (Figure 2) to 24 hours[35,37,51,54,57,101]. Fresh cadaver kidneys preserved for eight to 12 hours by this method resumed their function after transplantation[47,49,54,58].

In another series of experiments we preserved dog kidneys by *gravity perfusion* with the same perfusate at 4°C. for up to 80 hours. Oxygenation was, in our opinion, not necessary because of the reduction of oxygen requirements to 5% at this temperature. The results indicate that with this method of preservation an ischemia tolerance of up to 48 hours can be obtained[113].

The same result was obtained with the *low-flow-perfusion* (perfusion pressure 10 mm.Hg., kidney flow 2-4 ml/minute) and a perfusate of 50% blood and 50% balanced buffered electrolyte solution with addition of low molecular dextran or albumin and heparin, respectively[30,55].

For *machine-driven perfusion-hypothermia* the same apparatus used for the normothermic perfusion can be employed, if the blood heat exchanger is replaced by a blood cold exchanger. The perfusate consists of about 50% blood, Ringer's solution, low molecular dextran, bicarbonate, a buffer substance, heparin and procain with the pH adjusted between 7.25 and 7.40. At temperatures below 10°C. the arterial pressure should not rise above 50 mm.Hg.

A combination of *low-flow-perfusion, hypothermia and hyperbaric oxygenation* has recently been shown to produce the longest renal ischemia tolerance—in some experiments up to 72 hours[2,98].

The Liver

The ischemia tolerance of the liver is less than that of other organs; the occlusion of the afferent liver vessels is tolerated for only 20 minutes. The resultant parenchymal damage becomes irreversible after 30 minutes[74].

The pig liver with a longer ischemia tolerance time is an exception. Thirty minutes after the pig's death, and under normothermic

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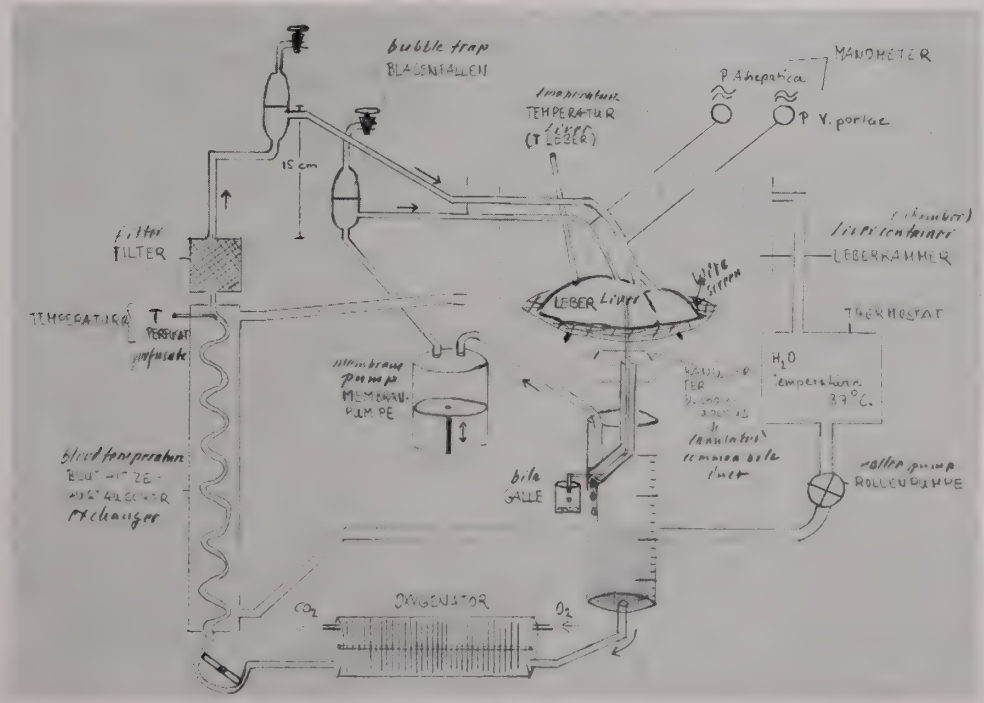


Fig. 3. Apparatus for perfusion of an isolated liver.

conditions, the liver resumed normal function with isolated perfusion[106,108].

It is possible, however, to increase the hepatic ischemia tolerance when hypothermia and perfusion by gravity are started in vivo[14,26,28,33,40-42,66,76,86,108], as also shown by our investigations[71]. We therefore recommend cooling of the liver before transaction or tying of the vessels.

Hypothermia and Hyperbaric Oxygenation

We have discontinued the use of simple hypothermia without perfusion in favor of a brief hypothermic gravity perfusion at 4°C. and subsequent storage in the refrigerator. The perfusate consists of Ringer's lactate solution with added albumin, low molecular dextran, glucose (as nutrient), a buffer and heparin. However, the efficiency of this method is limited[41,42,55,86,108].

Cooling below the freezing point, but without ice crystal formation, by using hydrostatic pressure or addition of dimethyl sulfoxide failed to prolong appreciably the ischemia tolerance of the liver. A partial success was obtained by dehydration of the liver by about 15% of its volume, at 2°C., and preservation of the organ by immersion in glycerol or dimethyl sulfoxide (-6°C.). In-vivo tests after heterotopic transplantation showed a limited function up to four days[10,14,50]. Organ preservation by freezing, however, has failed; in spite of protective measures taken, freezing damage has occurred.

Storage of the gravity-perfusion-cooled organs in a closed container, charged with oxygen under high pressure, increases the ischemia tolerance[14,33,35,41,42,54,57,58,86]. The effectiveness of this method depends upon the organ thickness and the applied pressure and is less in the liver than in other organs.

Perfusion

The reestablishment of the function in a transplanted liver which was preserved for more than six hours by normothermic perfusion has as yet not been reported. It is presumed that the organs were cooled before and after perfusion[6,26,27,33,53,61,66,76,86,91]. Our own dog experiments also failed to exceed this time limit[71]. We cannulated the hepatic artery and portal vein; the hepatic vein was allowed to drain. The perfusion system had two power sources. The hepatic artery perfusion was kept pulsatile by pump at 100/70 mm.Hg. pressure. For the perfusion by gravity of the portal vein the perfusate was elevated 15 to 20 cm. above the liver. The perfusion system was completed by the addition of an oxygenator, a heat-exchanger, two thermometers, two manometers, two bubble traps, a filter and a reservoir which could be used as a flow meter. The connecting parts were made from siliconized Tygon tubing. The bile flow was diverted and the amount replaced. The organ container was made from V-2a-Steel (stainless steel-Ed.) with an inner and outer thermo-insulating coat. A device was attached for introducing hyperbaric oxygen (Figure 3). Similar chambers have been described by others[28,34,42,66,76,86].

In the center of the slanted container bottom was the outflow spout for blood from the hepatic vein and for the bile drainage catheter which was inserted in the common bile duct. The inlets for the hepatic artery and portal vein were located on the lateral wall of the organ container. Both cannulae were connected to a manometer. The liver rested on a fine wire screen. Prior to hepatectomy the hepatic artery and portal vein were cannulated. After ligation of these structures they were perfused by gravity with low molecular dextran and sodium bicarbonate at 4°. A cholecystectomy was done and the common bile duct was cannulated. Eight to 10 minutes were needed for connection with the perfusion system. Gravity perfusion was continued during this time. The solution used in the extracorporeal liver perfusion with the oxygenator-pump consisted of 50% autologous blood, 20-30% Ringer's lactate, 10-15% low molecular dextran, sodium bicarbonate and heparin. The amount of bile produced during the six-hour perfusion varied between two and 10 ml/hour.

Hypothermic perfusion, particularly in combination with hyperbaric oxygenation, results in an additional prolongation of the ischemia tolerance time. The perfusate should contain not more than 50% blood, and the perfusion pressure should be stabilized below the physiological level[12,42,55,98]. The continuation—or the beginning—of the hypothermic extracorporeal circulation after death is a similar method of liver preservation. This was done for the first

time on heart surgery patients who could not be resuscitated[47,60,61,63,90]. To this day all human liver transplants have been preserved by this method. The longest period of ischemia was eight and one-half hours and the transplant functioned for several days[1,90]. By the combination of hypothermia, addition of metabolic suppressants, hyperbaric oxygenation and low-flow perfusion it was possible to increase the ischemia tolerance time of the liver from 48 to 72 hours[12,55,98].

Translated by: Emil Schleicher, Ph.D.

Summary

The various methods of organ preservation for transplantation are described. Our experimental and clinical experience with the preservation of kidney and liver is compared with reports from others. The limitations of the individual methods of preservation and their potential for improvement are discussed. In animal experiments the kidney and liver preservation was extended from 48 to 72 hours.

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Sardonic Humor

Apothecary: the physician's accomplice, undertaker's benefactor and graveworm's provider. *Diaphragm:* a muscular partition separating the disorders of the chest from the disorders of the bowel. *Childhood:* the period of human life intermediate between the idiocy of infancy and the folly of youth—two removes from the sin of manhood and three from the remorse of age.—Ambrose Bierce

Editor's Note: A brilliant but bitter journalist who disappeared into war-torn Mexico in 1914 probably found the euthenasia he desired.

If a man's curve of efficiency is ascending at 45, and keeps on ascending just after that period, it may well move upward for his whole life; but if there is a turn downward at 45, he will never recover.—Nicholas Murray Butler

---

Whatever a man's age, he can reduce it several years by putting a bright-colored flower in his buttonhole.—Mark Twain

Does Education Pay

Does education pay? What a question!

Does it pay to prepare the ground before sowing the seed?

Does it pay to polish the precious stone before putting it on the market?

Does it pay to plane and sandpaper the board before putting it into the piece of furniture?

Does it pay to sharpen the tools before working with them?

Does it pay to know things rather than live in ignorance?

Does it pay to have a mind rather than be a mere animal, and be directed by those who have minds?

Does it pay to think, and if so, to think with a trained mind rather than with an untrained one?

Does it pay to be a leader rather than a follower?

Does it pay to make the most of the faculties God has endowed one with, or to let them lie dormant?

Does it pay to be one of the capable of the human race or to be one of the inferior?

Does it pay to prepare oneself to do large things or to remain satisfied to do small things, and let others take the advanced positions?

Does it pay to take advantage of opportunity and make the most possible of oneself?

Does it pay to get an education? Only the lazy and the ignorant answer, "No."

Pay? Surely it pays—manyfold. There can be no better investment nor one anywhere near as good.

Let no youth be deceived. Ask those who are educated. Ask the wise of any generation. Be sensible. Get the education while you have the chance. Prepare to live a happy and prosperous life.

—Ward H. Nye, Superintendent of Schools, Billings, Montana.

Doctor

I remember when I grew up in the little town of Woodville, just north of Beaumont in the pine woods of eastern Texas, when we needed a doctor for a member of the family, we called Dr. So-and-So. If a cow was sick or one of the horses or even a pig, we usually called the same doctor.

But now when you go to see your family physician, you probably will wind up having a specialist recommended to you. A friend of mine did that, in this changing world, a few days ago, and the specialist recommended was a skin specialist. And he went over to the specialist who said, "Let me see your hands."

And he looked at them and said, "Yes, yes, yes, I see. Have you ever had that before?"

And the man said, "Yes."

And the specialist said, "Well, you've got it again."*

*Allan Shivers, Governor of Texas

Importance of Early Diagnosis of Renal Tumors

W. VAHLENSIECK, M.D.*
ST. GÖDDE, M.D.*
Bonn, West Germany

WITH THE DEFINITELY increasing incidence of malignancies[1] the frequency of renal tumors is also observed. Early diagnosis is very important for a favorable prognosis especially because curative radical surgery is superior to cytotoxic substances and radiation therapy. It is important to recognize the early symptoms of renal tumor; whenever any doubt exists, it is better to undergo extensive testing rather than wait for a definite sign, because the tumor may then have reached an incurable stage.

Our observation of 204 histologically verified tumors of the kidney, correlated with a careful study of case histories, showed that early symptoms were sometimes neglected by the patient or the doctor; or because of being nonspecific they were misinterpreted in favor of the overemphasized "cardinal symptoms:" gross hematuria, pain, and a palpable mass. These signs are late and may not always be found in patients with parenchymal tumors of the kidney. In our study gross hematuria was found in 49.6% of cases of advanced hypernephroma.[6] From the data of other authors gross hematuria does not occur in half of all the renal cases.[11,10,16]

Late Signs and Symptoms

Absence of Hematuria

Causes for late occurrence or complete absence of gross hematuria in renal tumors have been collected and recorded[6]:

1. Causes in tumor itself or surrounding the tumor (Figure 1):
   a. Peripheral localization of the tumor with centrifugal expansion
   b. Central localization, having capsule that prohibits expansion and infiltration
   c. Growth within a cyst
2. Extrarenal causes (Figure 2):
   a. Congenital or acquired stenosis of the ureter

*Surgical Clinic, University of Bonn, Department of Urology. Director: Professor A. Gütgemann, M.D.

b. Obstruction of ureter by blood clots, particles of tumor or calculi
c. Occlusion of lower urinary tract due to obstruction or combination of obstruction plus stenoses.

Dysuria

Dysuria, which would guide the patient to a urologic examination and diagnosis, occurs rather infrequently.

Absence of a Mass

In cases where gross hematuria is missing due to peripheral localization of the tumor or due to the development of a tumor in a fibrous-inflammatory capsule or in a cyst, the tumor may have a tendency to slower growth and be impalpable because of the inhibiting capsule.

Contrary to carcinoma of the thyroid or of the breast, renal tumors are not noticed by the patient in their early stages, due to their anatomical position or because of obesity; though in patients who are not obese and providing that the abdominal wall is completely relaxed, smaller renal tumors may be detected by bimanual palpation. Without hesitation a "palpable mass" should be considered as a late sign of tumor.

Pain

Pain as a symptom in renal tumors is not a constant complaint and was missing in 22% of all cases analyzed. It is understandable when we remember that pressure pain or neuralgic-like complaints start only when the tumor has grown large enough to cause increased pressure in the calices, increased tension of the renal capsule, or pressure on surrounding organs; or when it has metastasized to lymph nodes or to the spine. Episodes of renal colic may be observed due to the passage of blood clots or particles of tumor tissue.

Other late signs giving clue to the diagnosis in our series[7] were spontaneous fractures due to metastases to the bone, hemoptysis due to lung metastases, varicocele in 11%, anemia in 40% of the cases, leukocytosis with shift to the left, and polyglobulinemia in 2 to 5% of the cases.

Early Signs and Symptoms

The question arises: are there really any early signs and symptoms that would prove significant enough to include them in the general examination of a patient?

Fever of Unknown Origin

Perhaps one of the earliest signs is a low-grade intermittent fever associated with absence of leukocytosis. Elevation of temperature is caused by seepage of tumor protein or protein metabolites into the blood stream.

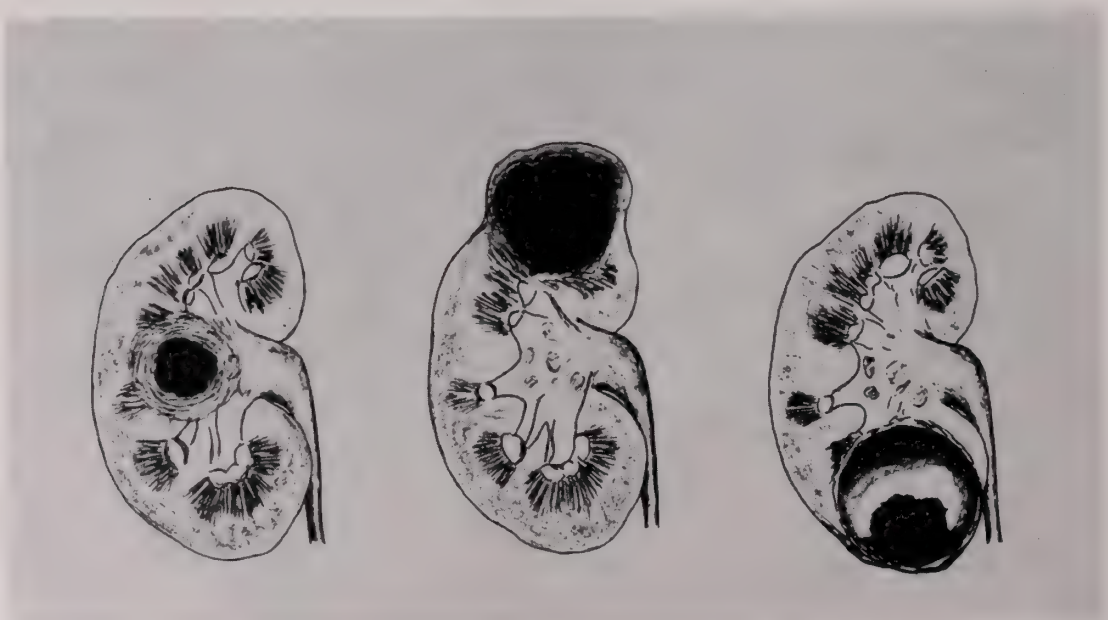


Fig. 1—Localization of tumors causing no gross hematuria.

Other causes may be associated with pyelonephritis or cystitis accompanied by typical pain or dysuria, which should aid in the differentiation. The incidence of early intermittent elevation of temperature occurred in 12 to 30% of cases. In our series the incidence was 12%. In several cases low-grade intermittent fever was the only symptom of a renal tumor. Other authors agree that the elevation of temperature ceases after nephrectomy.[2,14]

Gastrointestinal Complaints

If gastrointestinal complaints cannot be explained by tests, the diagnosis of renal tumor should be considered; in this series six patients had prolonged testing, treatment and observation for gastrointestinal complaints before diagnosis of renal tumor was made. This is a low percentage and possibly coincidental, as these complaints are difficult to explain on the basis of renal tumor. However, they should be considered when discussing the early diagnosis of renal tumors.

Diastolic Blood Pressure

Elevation of the diastolic blood pressure due to some renal factor is found more often.[8] In this and other[12] series marked elevation of blood pressure was found in approximately 22% of cases. In patients with Wilms' tumor diastolic pressure was found to be elevated in 50 to 75% of the cases.[3,9,13] It should be considered an important sign and an early symptom for the diagnosis of renal tumor.[15]

Microhematuria

As a rule, in all cases of malignant renal tumors grossly clear urine shows early microhematuria. Evans, Riches et al. and Staehler found erythrocytes in the urine in 80 to 100% of cases. Even in early stages it is demonstrated by repeated examination.

In our series microhematuria was demonstrated in 87% of the cases. It is due to stasis of venous blood resulting from compression of the parenchyma by tumor and by local inflammatory changes and secondary infection in the renal pelvis.

Elevated Sedimentation Rate

In our series the elevated blood sedimentation rate was found to be a very significant and important clue for the diagnosis of renal tumor; in almost all cases elevation of the blood sedimentation rate was demonstrated in one- and two-hour readings. In these cases renal tumors were always considered, especially if elevation of the blood sedimentation rate could not be otherwise explained. Though this is a nonspecific test, the difficulty of ruling out other causes and seeing most of our patients in the late stages of renal disease, we consider an elevation of the blood sedimentation rate an indication for thorough and complete investigation for renal tumor if no other explanation can be found.

Comments

From these facts it can be concluded that the early symptoms are very few and nonspecific; however, early diagnosis and a favorable prognosis can be achieved only by observing these early signs and pursuing them with specific diagnostic tests. Technically well performed x-rays of the kidneys will frequently

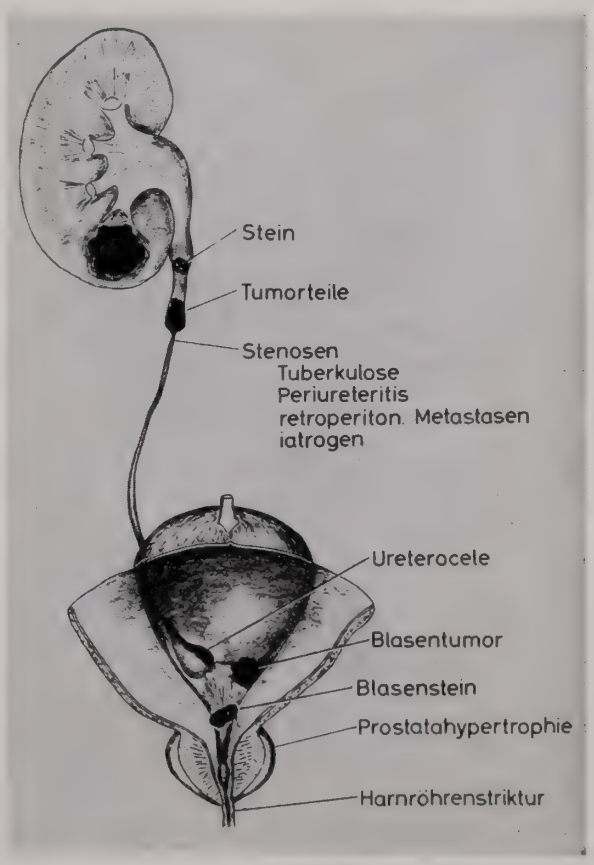


Fig. 2—Extra-renal causes for absence of gross hematuria: obstructing calculus, tumor tissue, stenosis, ureterocele, bladder tumor, bladder stone, prostatic hypertrophy, and stricture of urethra.

detect even the peripheral tumors by showing a distortion of the renal outline. As a rule small renal tumors may be demonstrated by large doses of intravenous contrast media, infusion pyelograms, tomograms or rate films.

In cases of doubt, renal scan may help the diagnosis, causing an insignificant amount of radiation. If even then doubt persists, retrograde pyelography and especially angiography is indicated.

Even if it is not always possible to differentiate between a cyst and a renal tumor, at least decision can be reached if surgery is indicated and an important step from early recognition to early treatment and better prognosis is made.

Conclusions

After observing 204 cases of parenchymal renal tumors with verified histological findings, conclusion is made that so-called *cardinal symptoms* — gross hematuria, pain, palpable mass, complaints caused by metastases, varicocele, anemia, leukocytosis with shift to the left, symptomatic polyglobulinemia—are observed in late stages. Statistics show that gross hematuria, due to tumor itself or surrounding causes or extra-renal causes, can be expected in only 50% of cases, and pain in only 22% of cases. Attention should be devoted to early signs like puzzling, intermittent fever (12-30%), unexplained gastrointestinal complaints, elevation of blood pressure (20-75%), microscopic hematuria (80-100%) and otherwise unexplained elevation of blood sedimentation rate.

If these symptoms cannot be explained by other means, special tests for renal tumor are indicated. By different diagnostic procedures, not significantly affecting the patient, early diagnosis should be achieved, leading to early treatment and a better prognosis.

Translated by: Rainis Berzins, M.D.

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Paean* to Health

Health, eldest of Gods, with thee may I dwell for the rest of my life and find thee a gracious house-mate. If there be any joy in wealth, or in children, or in that kingly rule that maketh men like to Gods, or in the desires we hunt with the secret nets of Aphrodite, or if there be any other delight or diversion sent of Heaven unto man, 'tis with thy aid, blessed Health, that they all do thrive and shine in the converse of the Graces; and without thee no man alive is happy.†

*Paean—a hymn of praise—paean: a metrical foot of four syllables, one long and three short.
†Ariphron 5th Century B.C.

With half an hour's reading in bed every night as a steady practice, the busiest man can get a fair education before the plasma sets in the periganglionic spaces of his grey cortex.—William Osler

Generosity is giving more than you can, and pride is taking less than you need.—Kahlil Gibran

Experimental Perfusion of the Pancreas

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A. BLOMER, M.D.*
R. SCHOLZ*
H. SEBOLDT*
Bonn, West Germany

IN TRANSPLANTATION of the pancreas, as in other organ transplantations, it is necessary to perfuse the excised organ during the ischemic phase. The proper composition and temperature of the perfusate prevent damage to the organ graft.

The pancreas poses particular problems due to the liberation of enzymes during operative manipulation, followed by autolysis.

The commonly used pancreas perfusate is dextran with added heparin. Glucose and procain adjusted to a pH of 7.4 is sometimes added[4] or small amounts of Trasylol[5]. Others do not use perfusation[1] but inject heparin solution into the vessels of the graft after transection.

The prevention of autolysis by the use of an enzyme-inhibitor during the operation and during perfusion of the excised organ is the principal problem, since acute pancreatitis may occur after manipulation and ischemia of the

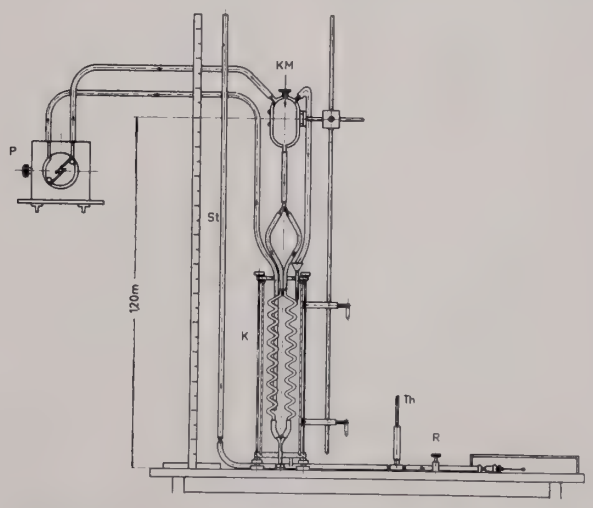


Fig. 1—Device for organ perfusion with controls for temperature, pressure and of low volume.

KM = Container for perfusate surrounded by cooling water.
K = Cooler.
P = Roller pump for cooling water.
St = Manometer.
Th = Temperature probe.
R = Regulating screw or flow volume control.

*Surgical Department of University Clinic of Bonn. Director: Professor A. Gütgemann, M.D.

organ. Greep[3] has shown that enzyme-inhibitors work best if administered before the pancreas is damaged. Once damage has occurred the efficacy of the enzyme-inhibitors diminishes in proportion to the time elapsed prior to its utilization.

Procedure

One hundred thousand units of Trasylol diluted in 250 milliliters of Rheomacrodex is injected into the donor animal during the operation. Immediately prior to excision of the organ the animals are heparinized with 5,000 International Units, in order to avoid clotting of the pancreatic vessels after transection. This method seems to be superior to the customary heparin perfusion after excision of the organ; with the latter method we have observed clotting in several instances.

Immediately after excision the pancreas is perfused through the celiac axis with a special solution:

Since the normally functioning pancreas metabolizes proteins we use an amino acid stock solution and add to each liter of 400,000 units Trasylol, 50 grams dextran, 10 ml Complamin and sodium bicarbonate in sufficient amounts to adjust the pH value to 7.35-7.40. The dextran aids the intravascular fluid retention and the Complamin prevents vasoconstriction. Only fresh solutions should be used, since they tend to become alkaline within three hours, at room as well as in cold temperatures.

We use gravity perfusion with a pressure of 120 centimeters water. The perfusion apparatus is shown in Figure 1. Its construction provides for a perfusate temperature of 2 to 6 degrees C; within these limits the temperature varies with the inflow volume. We found that a flow volume of 75 ml/min corresponds predictably to a temperature of 4 degrees C at the outlet. This flow volume proved to be optimal for a pancreas of dogs

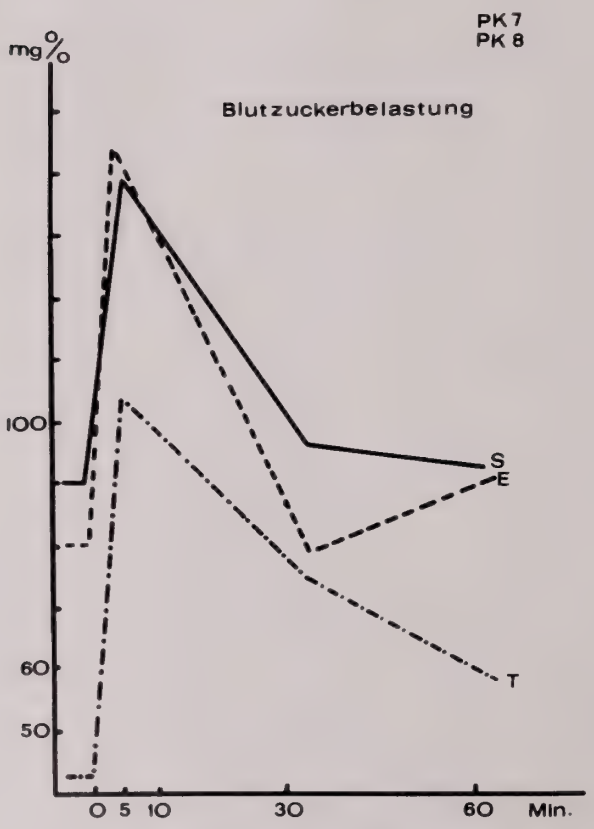


Fig. 2—Blood sugar tolerance curve after intravenous injection of 3 gr. dextrose in donor and recipient dogs, fasting.

——— S = Donor dog before operation; ···· E = Recipient before transplantation; -.-.-.- T = Transplanted pancreas six days after the operation.

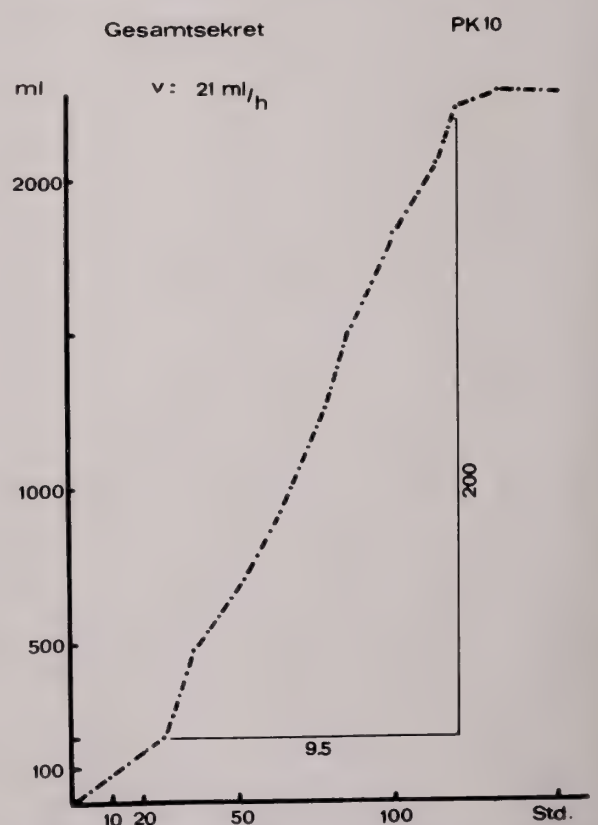


Fig. 3—Total secretion of the transplanted pancreas 130 hours after the operation.

weighing from 15 to 20 kilograms. When the flow is increased one occasionally sees tissue infiltration. In these instances, however, we found no evidence of impaired pancreatic function as compared with transplants which have undergone perfusion with lower volumes.

Results

Numerous determinations of intracellular sodium and potassium content in pancreatic tissue were made both before and after perfusion. We found no significant differences; there was also no change in O_2-consumption.

The grafts which did not receive immunosuppressive therapy secreted for six to 19 days if the animal survived initially. The longest period of function in a graft was seen in a dog which survived two and one-half months.

The incretory* function in isotopic pancreas grafts was determined by glucose tolerance tests; the excretory function was tested enzymatically in the fistula secretions (Figures 2 and 3). A comprehensive report of our methods of pancreatic homografting will be reported elsewhere.

Summary

A method of pancreas perfusion is described, using amino acid stock solution and an enzyme-inhibitor as perfusate, which replenishes proteins metabolized by the pancreas and neutralizes liberated enzymes.

We failed to see any acute pancreatitis or its sequelae with this method of perfusion in 16 transplant operations.

Translated by: H. W. Heupel, M.D., Ph.D.

*See Test Your Word Score, page 1583.

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Mail-Order "Health"

"No other country in the world begins to approach our national use of direct selling by mail. The public has amazing confidence in products so advertised. . . . The quacks with their nostrums, the miracle makers who can bring new sexual vigor to old men, grow hair or make it 'permanently' vanish, develop the bust, cure every ill from cancer to hemorrhoids, produce pills to make skinny people fat or fat people skinny, persist in their efforts, but we believe we have made the going considerably tougher. . . . The promoters of these schemes always think up a new wrinkle when we put them out of business, and it is amazing the diversity and the novelty of the schemes that are involved."—Abe M. Goff, General Counsel, Post Office Department, 1957.*

*James Harvey Young: The Medical Messiahs: A Social History of Health Quackery in Twentieth-Century America, 1967.

Prejudices

There is nothing to be said against the retention of prejudices. I believe in every man having a good stock of them, for otherwise we should be flimsy, ineffective creatures, and deadly dull at that.—John Buchan

Biogenic Stimulant

Athletes were objects of unusual and highly instructive experiments (at the Odessa Institute). And it turned out that there was a close connection between a foot race and biogenic stimulants. Filatov and his associates found this connection.

The eyesight of the runners was examined just before the starting gun. The race began, and after the runners crossed the finishing line their eyesight was examined again. It had become sharper. The scientists wanted to know why. The runners had not had any transplantations. They had not had injections. No biogenic stimulants had been introduced into their systems.

A simple experiment helped the scientists to get to the bottom of the riddle. After the race a few drops of blood were taken from one of the runners, and dissolved in water. The solution was injected into another person who had not run in the race, and had been sitting quietly in his laboratory. His eyesight improved.

Clearly, this happened because the blood taken from the runner contained substances that improved the eyesight. They must have appeared in the blood during the race—a product of intense muscular effort.

More blood was taken from the runners to determine the nature of these substances. Liquid extracts of this blood were tried in test subjects. The check-up revealed that their properties and effects coincided with those of biogenic stimulants.

This led to a new conclusion: Work increases the output of biogenic stimulants. Work, therefore, is a physiological necessity, and is beneficial to the system. Filatov says that "by working not only mentally, but physically as well, a man tones himself up and raises his psychophysical level."*

*L. Fridland, M.D.: The Achievement of Soviet Medicine, 1961. Edited and translated by W. Horsley Gantt, M.D.

The Tongue-Scraper

I think more of this little implement (the tongue-scraper) on account of its agency in saving the Colony at Plymouth in the year 1623. Edward Winslow heard that Massasoit was sick and like to die. He found him with a household of people about him, women rubbing his arms and legs, and "friends making such a hellish noise" as they probably thought would scare away the devil of sickness. Winslow gave him some conserve, washed his mouth, *scraped his tongue,* which was in a horrid state, got down some drink, made him some broth, dosed him with an infusion of strawberry leaves and sassafras root, and had the satisfaction of seeing him rapidly recover. Massasoit, full of gratitude, revealed the plot which had been formed to destroy the colonists, whereupon the Governor ordered Captain Miles Standish to see to them; who thereupon, as everybody remembers, stabbed Pecksuot with his own knife, broke up the plot, saved the colony, and thus rendered Massachusetts and the Massachusetts Medical Society a possibility, as they now are a fact before us. So much for this parenthesis of the tongue-scraper, which helped to save the young colony from a much more serious scrape, and may save the Union yet, if a Presidential candidate should happen to be taken sick as Massasoit was, and his tongue wanted cleaning,—which process would not hurt a good many politicians, with or without a typhoid fever.*

*Oliver Wendell Holmes

The Pulmonary Vascular System

Problems in Anatomy and Hemodynamics

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A. DUX, M.D.*
E. BUCHELER, M.D.*
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OF ALL ORGANS the lung is the only one whose vascular system accommodates the entire cardiac output. Therefore a method of determining the functional cross-section of the pulmonary vasculature is of particular interest.

Problems

The direct determination of the anatomy of the pulmonary vascular system is possible only by angiographic methods. By means of the so-called selective and terminal angiograms[1-5,10,17,18] we are enabled to assess the function of terminal pulmonary vessels and to observe rarefactions and constrictions, especially in the precapillary and capillary vasculature.

The Flow Velocity

The pattern of distribution and flow velocity enables us to derive the cross-sectional distribution within the precapillary and capillary beds. Normally the flow velocity diminishes geometrically with an increase of the cross-section. Bolt, Rink and Semisch found that a reduction of the capillary cross-section results in a lowering of the flow velocity in the small arteries and arterioles, while the contrast medium traverses the capillary field with increased velocity. This important observation leads to the assumption that in the presence of tissue loss, as in pulmonary emphysema, there is a changing cross-sectional distribution between capillary, precapillary and arterial space. Thus the tissue loss affects the capillary system more than any other. The loss of alveolar walls first affects the capillary field[18]; the precapillaries and arterioles are involved only at a later stage. The redistribution of hemodynamic and geometric cross-sections, however, is not affected by these changes.

Vascular Capacity

While selective and terminal pulmonary an-

*From The Institute for Radiology and Radio-Therapy, Director: Professor Dr. P. Thurn, and from The Department of Surgery, Director: Professor Dr. A. Gütgemann, University of Bonn.

giography permits an estimation of the hemodynamic cross-section, it is still impossible to assess the elasticity and reactivity of the pulmonary vessels. A change of the cross-sectional area within the vascular system can neither be provoked nor be measured locally. A determination of the extent of vascular cross-sectional regulation makes it possible to relate a given cross-sectional measurement to the possible limits of vascular reactivity. Variations in pulmonary vascular capacity have been repeatedly found,[18,11] and they explain changing circulation times in the same pulmonary system with identical pulmonary artery pressures.

Observations

Vasoconstriction in the Lung

The first goal in evaluating the pulmonary vascular system should be an approximate determination of the pulmonary vascular cross-sectional area and of its maximal and minimal values. Reversible change of the cross-sectional area in the pulmonary vasculature and its

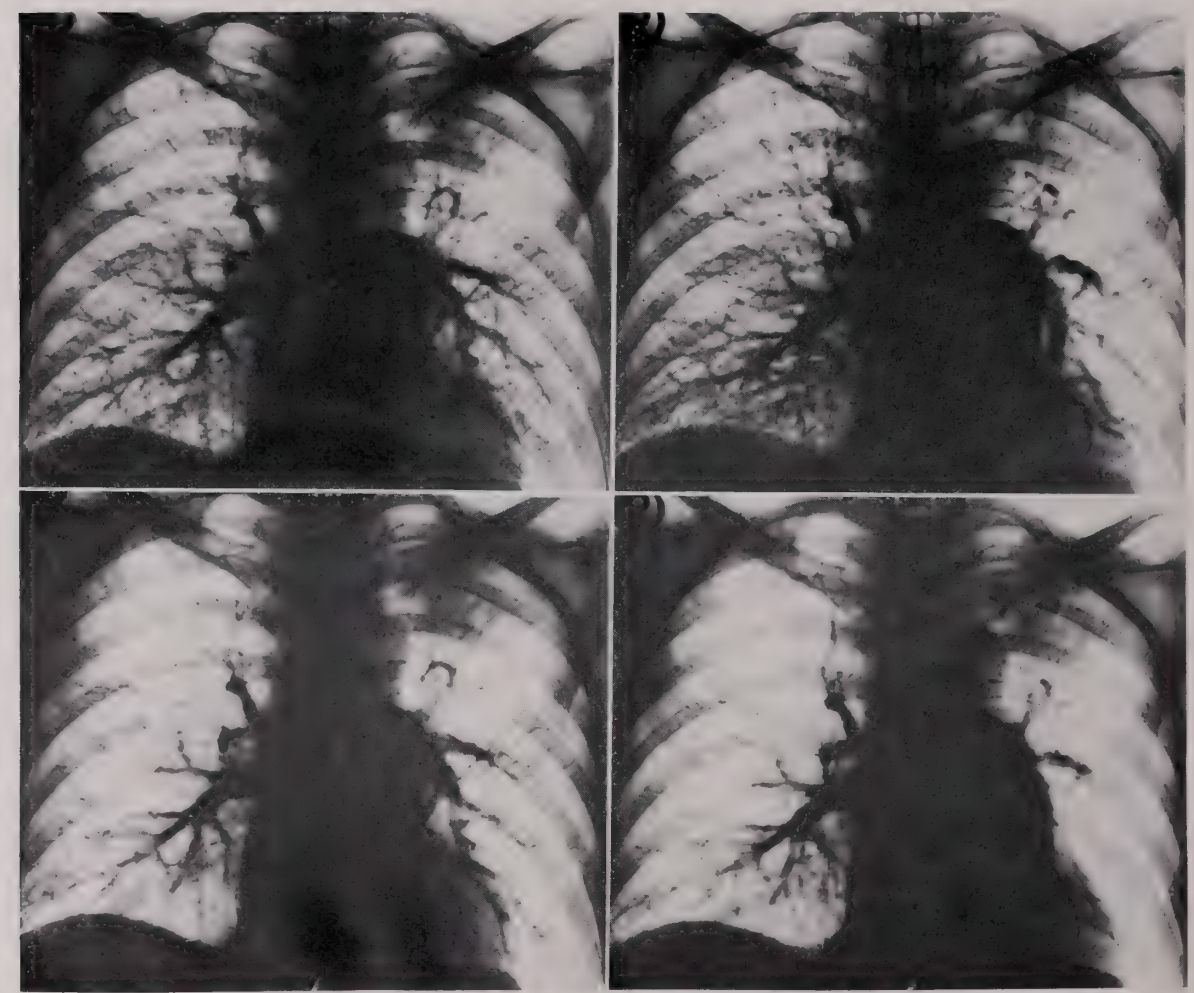


Fig. 1—Fifty-year-old female with bronchial carcinoma in the apical segment of the left upper lobe.

(a and c) Pulmonary arteriogram during normal ventilation under Fluothane anesthesia.

(b and d) Pulmonary arteriogram during suspension of ventilatory diffusion of the left side during Fluothane anesthesia; 66% of the heart minute volume passes the right and 34% passes the left lung.

(a) Uniform vascular density and vascular diameters in both lungs, showing no difference in radiolucency and flow velocity.

(b) Identical phase of dye passage as in Figure 1a. Distinct functional rarefaction of the vessels and diminution of vascular diameters on the left side. "Functionally hyperlucent lung" left.

(c) Early arterial phase (2 seconds before Figure 1a). Bilaterally equal inflow velocity of blood contrast medium mixture.

(d) Identical phase of contrast medium passage as in Figure 1c. Distinct diminution of inflow velocity on the left side as compared with the right.

determination has been shown and described by us in previous publication.[8,9] Figures 1a and 1b depict such localized cross-sectional change. In Figure 1a the vascular cross-sections of both lungs are practically identical, whereas Figure 1b shows a distinct rarefaction of vascular density and decreased arterial width in the left lung indicating an effective vasoconstriction in that lung.[6] This phenomenon was discovered by Euler and Liljestrand and has been named "alveolo-vascular reflex" by Rossier and coworkers. It connotes an inter-relationship between alveolar gas pressures and hemodynamic resistance. We have defined the result of this reflex as the "functionally, unilaterally hyperlucent lung."[9]

Recognition of this phenomenon by angiographic means resulted in the discovery of a second phenomenon: the redistribution of linear flow velocity between both lungs. Figure 1c demonstrates a bilaterally equal inflow-velocity of the blood-contrast-medium mixture, while Figure 1d shows a distinctly diminished inflow velocity into the left lung during a provoked cross-sectional reduction. According to the law of Hagen-Poiseuille the flow through a tube varies with the fourth power of the radius. The velocity of flow is defined as the quotient of flow over the time unit over the cross-section. Thus in the presence of parallel vessels a reduced cross-section results in a reduced flow velocity.

A comparison of Figures 1d and 1c definitely proves the validity of this theory: 66% of the cardiac minute volume passes through the right lung and 34% through the left lung during the phase depicted in Figure 1d.

Changing Alveolar Gas Tension

Selective angiography should be able to demonstrate vascular changes in response to changing alveolar gas tensions as long as these reactions occur homogeneously in all segments. However, such homogeneous reactions are quite rare. Emphysematous changes in the elderly usually occur in uneven distribution patterns, resulting in a mixed picture of more or less emphysematous deformation. Since the changes of the vascular cross-sectional areas parallel the development of emphysema in the different regions of the lung, the findings of a limited cross-sectional vascular area are not necessarily representative of the entire lung.

Figure 2 is a typical example of a vascular

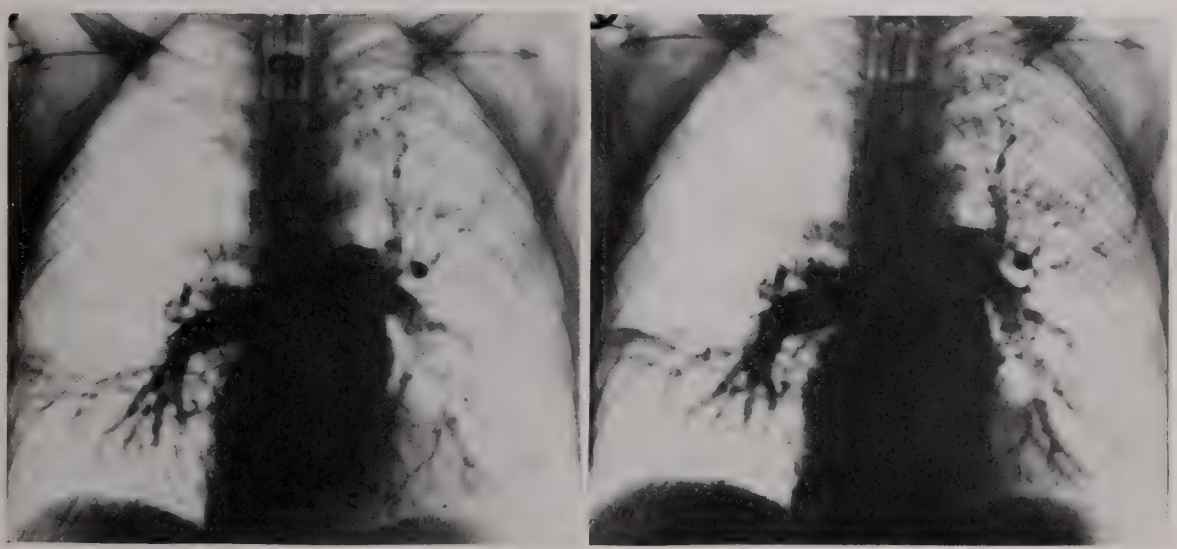


Fig. 2—Fifty-year-old male with bronchial carcinoma in the anterior segment of the right upper lobe. Primary vascular rarefaction in the enlarged right upper lobe, due to emphysema and tumor. Emphysema also present in the left lower lobe.

(a) Pulmonary arteriogram during normal respiration under Fluothane anesthesia. Approximately even vascularization in the right lower and the left upper lobe.

(b) Pulmonary arteriogram during right-sided suspension of respiratory gas diffusion under Fluothane anesthesia; 82% of the cardiac minute volume passes the left and 18% passes the right lung.

Functional vascular rarefaction in the right lower lobe. Increase of vascular density in the left upper lobe. Unchanged findings in the left lower and right upper lobe.

reaction to a change of alveolar gas pressure; Figure 2a shows the primary vascular cross-sectional reaction in this lung. The vessels in the enlarged right upper lobe are rarefied due to tumor and emphysema. Advanced emphysema is also seen in the left lower lobe.[13] If the vascular system of the right lung is exposed to equilibration of the alveolar gas pressures to the mixed venous level, then a reduction of the cross-sectional area in the right lower lobe can be noted (Figure 2b). This corresponds principally to the reduction in the left lobe shown in Figure 1b, although to a smaller degree. A further narrowing of the vasculature in the right upper lobe is obviously impossible. While in Figure 2a the vascular density is about equal in the right lower and left upper lobes, it is distinctly different in Figure 2b. Here the reduction and cross-sectional area at the right lower lobe has been largely compensated by the left upper lobe. Areas with more marked emphysematous changes in the left lower lobe are incapable of these compensatory reactions.

Figure 2b shows the entire lung of this patient is composed of four different vascular areas which react differently. This multiplicity of behavior cannot be captured by selective angiography, which is incapable of registering the constrictive capacity of the pulmonary vasculature as well as of providing a general picture of the pulmonary vasculature. During the circulatory phase shown in Figure 2b, 82% of the heart minute volume passes through the left lung and 18% through the right lung.

Figure 2 illustrates another pathophysiological problem. The changes in the left lower lobe seen in Figure 2a may be an expression of alveolar hypoventilation with the resulting changes in alveolar gas tensions. If in these cases the observed vascular constriction is of a functional nature,[7,12] it will disappear when a vascular constriction is induced in the contralateral lung. By reacting in this fashion the normally ventilated lung demonstrates an adequate cross-sectional vascular reserve which enables it to accommodate the increased flow and the increasing vascular distention factor. Organic and functional vascular constrictions in the normally ventilated lung can thus be distinguished.

In the case shown in Figure 2 the cross-sectional areas are morphologically "fixed." Morphology alone does not suffice for a certain differentiation between functional and organic constriction. However, the capacity of the pulmonary vascular system to alter the cross-sectional diameter is of great importance in the preoperative assessment when a pneumonectomy is planned.

Influence of Age

Angiographic evidence indicates that the capacity of cross-sectional vascular regulation diminishes with increasing age; however, this does not exclude the possibility of persistent reactivity of the arteriolar and precapillary vasculature. This can be shown by indirect means. A 69-year-old male patient with a bronchial carcinoma of the left upper lobe serves as an example. Figure 3 shows definite rarefaction of the vasculature of the left side and emphysema in the right upper lobe. When the alveolar gas diffusion is interrupted, as shown in Figure 3b, there is only a very moderate rarefaction of the vasculature. The interdependence of the hemodynamic cross-section and flow velocity again becomes evident in both lungs toward the end of the passage of the contrast media. Figure 3c shows a uniform distribution of dye in the central veins in the presence of unchanged pulmonary hemodynamics. If, however, the gas diffusion is abolished (Figure 3d) the passage of contrast media in the normally ventilated right lung is already completed while there is still filling of the central veins of the left side similar to Figure 3c. A decreased diameter of the dye-filled veins on the left side is also noticeable, in comparison to Figure 3c.

Our experience with 75 patients indicates that this marked difference in flow velocity cannot be caused by the relatively small change in cross-sectional area in those vessels which are demonstrable by angiographic means. Cross-sectional changes in the arteriolar precapillary segments which occupy a much larger cross-sectional area have greater influence on the resistance and thus on flow volume and flow velocity. Therefore, we assume that there is a sufficient reactivity of the arteriolar segments persisting in this patient.

The third example also shows that a reduction in vascular cross-sectional surface, be it of

organic or functional origin, does not exclude further vascular reactivity.

Clinical Application

Risk of Operation

In deciding on a pneumonectomy the question arises whether or not the remaining lung can accommodate the entire cardiac output while maintaining a normal pressure head.[1-5,17,18] Advanced emphysema is usually accompanied by functional and morphological diminution of the pulmonary vascular bed,[12,16] and the operative risk in pneumonectomies is thereby increased. Complete excision of a lung tumor would be ill-advised if it should lead to irreversible right heart failure.[17,18]

Postoperative Prognosis

The commonly used pulmonary function studies, such as spirography and blood gas analyses, demonstrate only the patient's preoperative condition. An attempt to gain some information for the postoperative prognosis is warranted. Selective pulmonary angiography[1-5,17,18] can demonstrate the vascular bed in selected areas at a given time and show the degree of emphysema. This method, however, is not suited for assessing the vascular cross-

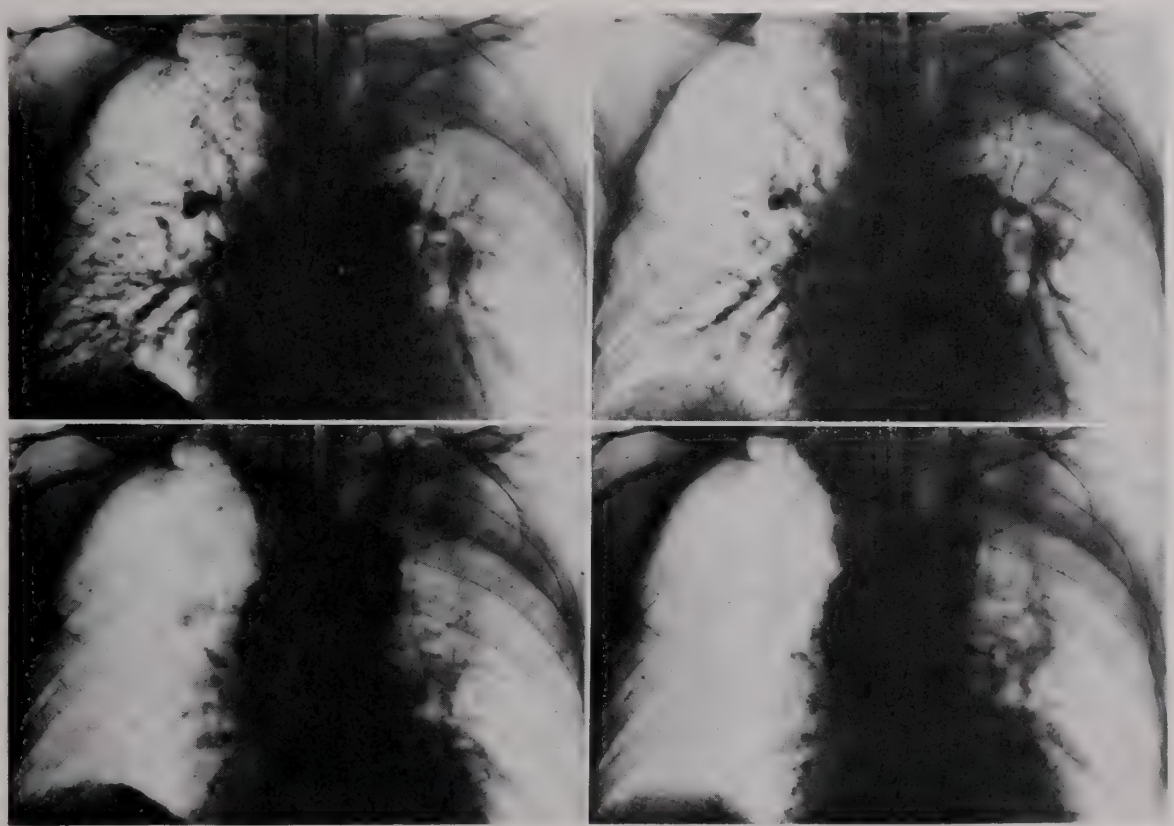


Fig. 3—Sixty-nine-year-old male with bronchial carcinoma in left upper lobe. Primary vascular rarefaction in left lung. Tumor compression of left-sided arteries of the apical and posterior upper lobe segments and of the main branch to the lower lobe artery.

(a and c) Pulmonary arteriogram during normal ventilation under Fluothane anesthesia.

(b and d) Pulmonary arteriogram during left-sided suspension of ventilatory gas diffusion under Fluothane anesthesia; 80% of the cardiac minute volume passes the right and 20% passes the left lung.

(a) Late arterial and early venous phase. Emphysema in right upper lobe.

(b) Identical phase of contrast media passage as in Figure 3a. Small increase of vascular rarefaction in the left lung. Only small increase of vascular density on the right side. Slightly increased inspiratory position as compared with Figure 3a.

(c) Late venous phase (2.6 seconds after Figure 3a). The large central veins are equally contrasted on both sides.

(d) Identical phase of contrast medium passage as in Figure 3c. On the right side the contrast medium passage is completed while there is still filling of the more central veins on the left side. The venous diameters on the left side are slightly diminished as compared with Figure 3c.

sectional surface and the vascular capacity. This capacity is the decisive factor for the postoperative fate of the right heart.

The Method of Pulmonary Angiography

Our method[8] consists of pulmonary angiography during unilateral suspension of alveolar gas diffusion. It shows the propensity of the pulmonary arteries and veins to change their diameter in response to the suspension of gas diffusion. A shift of a portion of the cardiac output from the non-ventilated to the normally ventilated lung would be impossible if the vascular diameter on both sides were fixed. The ability of the pulmonary vascular bed to dilate or to constrict can be seen simultaneously in both lungs.

The vascular diameter in the pulmonary bed diminishes with progressive tissue loss and all vascular reserve may perish. A functional reduction of the vascular pulmonary bed becomes impossible and pulmonary perfusion with the normal cardiac output then brings about increased pulmonary artery pressures in order to maintain flow. The increased intravascular pressure results in increased wall tension. The angiographic demonstration of marked functional decrease of the vascular cross-sectional area indicates the absence of marked pressure increases in the pulmonary vascular bed, which means that there is a compensatory capacity of the vascular cross-sectional area. The exact pulmonary artery pressures at which cross-sectional regulation ceases is still to be determined. This pressure depends also on the elasticity of the vessel wall.

The determination of oxygen consumption and blood gas analyses during suspension of ventilatory diffusion in one lung, while the other lung is normally ventilated, enables us to judge the efficiency of the ventilated lung and to calculate the shift of the cardiac output.[8]

Summary

Selective pulmonary angiography during normal ventilation does not permit a complete assessment of the morphology and function of the pulmonary vasculature. The structure and function of the pulmonary vessels vary greatly throughout the lung, especially in older people with emphysema and bronchial carcinoma. The demonstration of all lung vessels and a simultaneous assessment of the capacity of pulmonary vessels to change their diameter in all portions of the lung permit us to judge the adaptability of the pulmonary vascular bed to marked flow changes and thus the fate of the right heart after pulmonary resection.

The extent of pulmonary vascular adaptability can be seen after unilateral suspension of respiratory gas diffusion without simultaneous mechanical impairment of the lungs, and this regulatory capacity permits predictions for the functional vascular diameters. It is possible to distinguish functional pulmonary vascular constrictions due to localized alveolar hypoventilation from anatomically fixed circumscribed vascular narrowing. The action and interdependence of physiological and pathophysiological parameters are discussed.

Translated by: H. W. Heupel, M.D., Ph.D.

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Ideas are like rivets. They should be driven home and clinched while hot.—Carbuilder

Cardiac Arrest in Children

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CARDIAC ARREST carries a much more ominous connotation in children and infants than in adults. While hereditary and circulatory diseases are the main factors in middle and older age,[2,4,10,16,24] children with normal hearts are more frequently victims of acute cardiac arrest than are children with heart disease.[14]

Twenty percent of the 1710 cases collected by Stephenson were children under the age of 10 years. Successful resuscitation was possible in 30% of all ages.[21,31] Children have a more favorable prognosis than adults.[31] It is a fact that acute cardiac arrest occurs more frequently during heart surgery than with other operations, and that resuscitation succeeds more frequently.[7] Therefore we have to concede a special place to cardiac surgery in any discussion of cardiac arrest and resuscitation.

Cardiac Arrest

Incidence

There were 18 children under 14 years in a group of 96 patients who suffered acute cardiac arrest while in our surgical clinic (Figure). Seven of them came to us with conditions that were directly responsible for the cardiac arrest: thoracic injuries, congenital atresia of the esophagus, aspiration of foreign bodies, other aspirations, tetanus.

Eleven children were admitted with benign conditions and only one child had to come to surgery because of appendicitis. Thus it appears that cardiac arrest was predominantly caused by exogenous factors. Our figures confirm that lack of oxygen was the primary reason.

Causes

One is easily deceived when dealing with cardiac arrest. Frequently one incriminates toxic or allergic factors (roentgen-contrast media, drugs, narcotics and digitalis prepara-

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tions), mechanical injury to the heart, cooling, changes in electrolytes, acid-base balance, bacterial toxins and neurogenic reflexes. We must recognize, however, that these factors rarely lead to cardiac arrest per se, but primarily to a respiratory deficit or blood loss (Table). Frequently these two forms of hypoxia are combined with other pathophysiologic mechanisms, which can not always be defined.

Case Report

A 21-month-old boy with perforated duodenum and peritonitis was prepared for surgery, when ventricular fibrillation occurred. The general condition of the child with peritonitis and a high degree of dehydration was grave. During pulmonary aspiration the respiration was handicapped by the distended abdomen.

Previously, while being transported to the hospital,

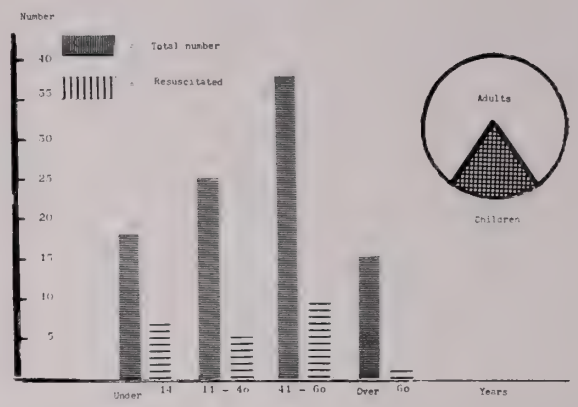


Fig. 1—Age distribution of 96 patients with acute cardiac arrest.

TABLE

No.	Age	Sex	Basic Disease	Circumstances of Cardiac Arrest	Causes	Cardiac Massage	Resuscitation
1.	21 mo	M	Perfor. duod. ulcer	Preparat. for surgery	asphyxia	ext.	died
2.	7 y	M	Tetanus - infection	Aspirat. of tracheal tube	asphyxia reflex mech	int. ext.	with defect
3.	3 y	M	Foreign body aspiration	During bronchoscopy	asphyxia reflex mech. ?	int.	died
4.	4 y	F	Cerebr. contusion rupt. spleen rib fractures pneumothorax rupture of mesenteric arteries	Bleeding from trach. tube	asphyxia hypovolemia	ext.	without defect
5.	11 y	M	Pneumothorax bronchial tear	Begin. of operation	asphyxia hypovolemia	int.	died
6.	8 y	F	Rupture of liver and spleen	During surgery	hypovolemia	int.	survived 2 hours
7.	10 h	F	Atresia of esophagus esophago-tracheal fistula	During surgery	asphyxia	int.	survived 4 hours
8	3½ y	M	Congenital stenosis of esophagus	At tracheotomy for atelectasis	reflex mech ? asphyxia	int.	survived 6 hours
9.	1 y	M	Congenital torticollis	During surgery	hypovolemia	int.	survived 18 hours
10.	2½ y	M	Congenital sub-luxation of hip	During surgery	not known	int.	died
11.	5 y	M	Hypospadia penis	Begin. of anesthesia	not known	int.	no defect
12.	4 y	M	Burn-scars	During surgery	not known	int.	no defect
13.	4 y	M	Megacystitis megaureter	During retrograde Pyelogram under anesth.	not known	ext.	no defect
14.	18 mo.	M	Cleft palate	After surgery	not known	int.	died
15.	10 y	F	Appendicitis	During surgery	not known	int.	no defect
16.	3 y	F	Bone cyst osteomyelitis	During surgery	hypovolemia	int.	no defect
17.	4 y	F	Lymphoma colli cysticum	At end of surgery	hypovolemia	int.	died
18.	2 y	F	Recurrent infections of UR tract	During surgery	not known	ext.	no defect

the child had received artificial respiration by mask, and resuscitation of the heart was accomplished by external cardiac massage. A subsequent pneumothorax necessitated a Buelau-drainage and, since the bronchial tree could not be cleaned sufficiently, a tracheotomy was performed. Finally respiration and circulation stabilized enough to permit abdominal surgery. After the operation another episode of ventricular fibrillation occurred but was successfully managed by external cardiac massage, defibrillation, and intracardiac injection of suprarenin-calcium; but when functional cardiac arrest recurred for the fourth time, all attempts at resuscitation failed.

Resuscitation

The advantages and disadvantages of the external cardiac massage is still the subject of many clinical and experimental studies.[6,9-12,19-21,23,25,28,32,33,36,38,39] The majority of authors favor external cardiac massage in infants or children. Even though all details of procedure have been worked out,[39] we think it advisable to indicate some directives which have been rarely mentioned.

All methods of external cardiac massage are physically exhausting, whether one uses the two-hand, one-hand, one-hand-thumb or two-finger method. The two-hand method is recommended for children of school age. The child should be placed supine on a rigid foundation. Placing a board on top of a mattress is insufficient as it will not prevent the yielding of the mattress. The rhythmic compressions of the sternum, which are meant to prevent a lateral escape of the heart, are thus less effective; likewise the compression is ineffective in spite of great expenditure of power. The patient should lie on the ground or on the floor. This is true also for the one-hand and the two-finger methods, which are more appropriate between the first and fifth year of life. In newborns and infants up to the age of six months we prefer the compression of the sternum between the two thumbs and the palms of the hands. The movements are symmetrical and applied vertically to the frontal plane of the body. The effort is thus distributed evenly to both hands and constant changing can be avoided. The resuscitation procedure should include: electrocardiography for differential diagnosis, electrical defibrillation, intracardiac injection of Alupent according to type of cardiac arrest, suprarenincalcium, adrenalin, potassium; also control and correction of metabolic acidosis, fluid replacement, and intravenous sodium bicarbonate.

Comments

Forced Breathing and Intubation

We saw in this child a sequence of complications, in which respiratory problems were prominent. It is well known that forced oxygen breathing can lead to distention and even rupture of the normal stomach.[27,37] Artificial respiration by mask is even more likely to emphasize and aggravate the pneumoperitoneum, which occurred in this instance from perforation of the duodenum. For this reason one ought to prepare for intubation as soon as ulcer perforation is suspected.

Tracheotomy

One should hesitate to employ tracheotomy because of the inherent complications in children.[1,5,18] A pneumothorax need not have dire consequences if it is recognized in time and corrected; but the mucopurulent tracheobronchitis, which often follows, should be taken seriously because it may complicate the maintenance of open respiratory passages. The intubation tube may be plugged at times by mucus, and atelectasis may occur within a short time. Even careful and intensive nursing with regular aspiration of the bronchial tree with soft curved catheters and utilization of the most modern aspiration or respiratory apparatus may not protect from the danger of atelectasis.

The cardiac arrest proper occurs during the introduction of the catheter, during the changing of tubes or during change of the child's position. Thus the importance of the so-called reflex cardiac arrest comes to mind.

Case Report

A nine-year-old boy with tetanus received mechanical respiration through a tracheotomy. During tracheobronchial aspiration through the tracheostomy asphyxia and cardiac arrest occurred.

Similar events, such as the introduction of a bronchoscope to recover an aspirated foreign body in a three-year-old boy, led to cardiac arrest.

These events remind us of an experiment by Sloan, to which Schwaiger[29,30] attributes fundamental importance: stimulation of the vagus in a dog led to cardiac arrest only when it fol-

lowed hypoxia. We believe with Tschirren, Nissen et al. that reflex cardiac arrest without other complications is rare during surgery.[17,26]

Hypovolemia

In six children cardiac arrest was preceded by hypovolemia (Table). While blood loss is easily overestimated in the adult[3] the opposite is true for children. It is not so much the obvious arterial hemorrhage which leads to hypovolemia, since it is easily recognized and remedied. The greater danger threatens children who bleed slowly, drop by drop, during procedures in which a substantial blood loss is not expected. All signs of imminent hypovolemia are difficult to measure in children.

Conclusions

Seven of the 18 children left the clinic after acute cardiac arrest in apparent good health and without central nervous system defects. In five of these children the cause of arrest had not been established. A citation of possible causes would serve neither prophylaxis nor therapy. We can only state that inadequacies have become apparent within our surgical domain (asphyxia, hypovolemia), which offer a basis for prophylactic measures against cardiac arrest.

Translated by: H. H. Zinneman, M.D.

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Synthesis of Greek and Christian

Looking back we can say that the Greek concept of health was primarily physical and that Greek hygiene was aristocratic. The Christian concept of health, on the other hand, was primarily spiritual and Christian hygiene was catholic, addressing itself to all. The synthesis of both, the development of a concept which would embrace physical and mental health without compromise, the revival, general adoption, and democritization of the *mens sana in corpore sano* of Juvenal—this ideal becomes the program of the ensuing centuries.*

*Henry Sigerist, M.D.: Medicine and Human Welfare, 1941.

The measure of success is not whether you have a tough problem to deal with, but whether it's the same problem you had last year.—John Foster Dulles

I was gratified to be able to answer promptly and I did. I said I didn't know. —Mark Twain

The Dissociated Brain Death

Clinical and Electroencephalographic Criteria for Determination of Death

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A COMPLETE FUNCTIONAL deficiency of the brain extending over several hours, the sequel to a transitory anoxemic injury after a traumatic brain damage or from severe metabolic anoxia is, according to past experiences, irreversible. Even if in this condition the circulatory system is stimulated by intensive reanimation for many hours or even days the eventual death of the individual is inevitable. Thus over a certain time period a dead brain, accompanied by a pulsating heart, can be spoken of as a dissociated brain death.

These experiences raise doubt with regard to the present concept of the clinical determination of the time of death, which, when oriented on the parameter of the heart function, is based on indirect signs of heart and circulation stoppage. Perhaps it is as correct to identify the death of the individual with the brain death as with the death of the heart[3,19,22,23] because of the reciprocity of brain function with physiological integrity. Consequently, an individual with a dissociated dead brain, in spite of a pulsating heart, must be declared dead.

In this article the scientific-biological problem, rather than the forensic, legal, moral and religious aspects, is presented.

Paramount and pertinent are three questions that must be considered together before death is declared when there is still a beating heart and one chooses to discontinue re-animation. (1) Is the dissociated brain death absolute, that is, unmistakable? (2) Can the determined nonfunction of the brain be reconstituted? (3) After what time is dissociated brain death absolutely irreversible?

Diagnosis of the Dissociated Brain Death

Clinical Definition

The clinical definition of cerebral death according to Schwab[22] includes: (1) deep coma with atony and absolute areflexia; (2) nonresponse to strong sensoric stimulation; (3)

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mydriasis with absolute pupil fixation; and (4) absence of spontaneous breathing.

A single registration of these symptoms is not sufficient, but a continuous observation over a certain period of time is necessary.

For the objective evaluation of the clinical and neurological findings various other examinations are available;[16,4,9,20] but these may not be wholly satisfactory.[5,25] Recent experiences have proven the electroencephalogram to be the most reliable instrument because it is the only objective method whereby brain function can be absolutely measured. The brain potentials and the modulation through subcortical influences are strongly reflected. In the case of death there is absolute cessation of the electrical potential and isometric curve pattern.

The isometry in the electroencephalogram, however, allows two interpretations: first, the sign of an irreversible loss of function (brain death), and secondly, the expression of a reversible functional block of the brain. Thus one does not conclusively know from the isometric curves which cerebral dysfunction is the cause of the cessation of electrical potential, although a differentiation is possible if one applies the old principle as defined in the preceding clinical picture. Thus the question of the time of brain death can be accurately determined when clinical symptoms of cerebral death are present.

Electroencephalographic Identification

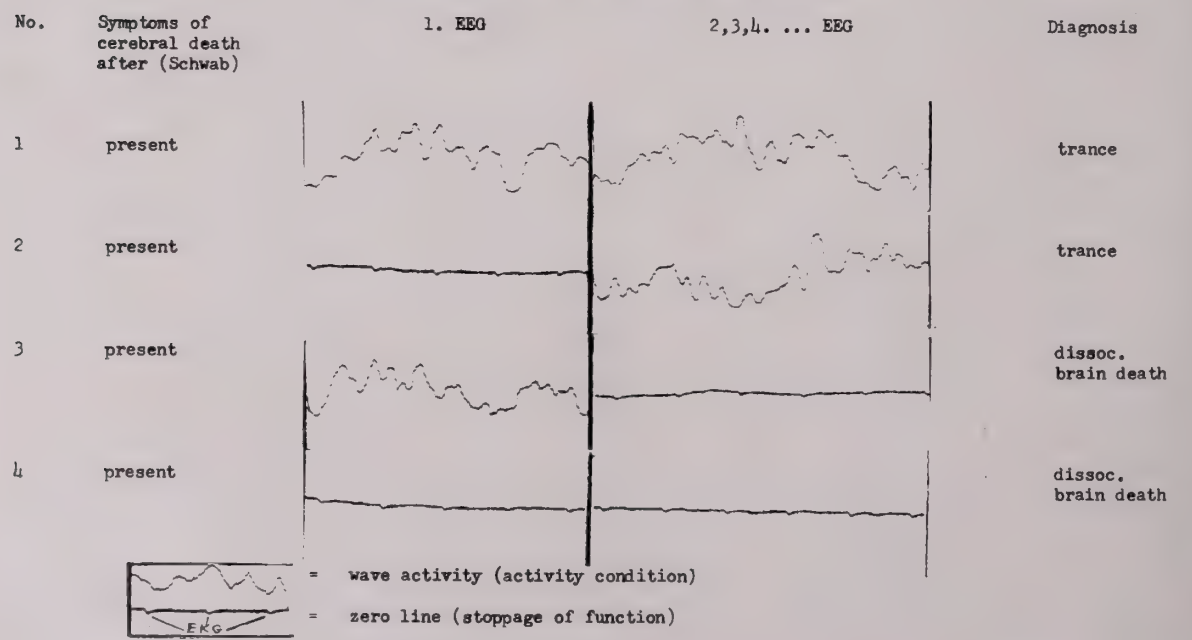
When these assumptions are fulfilled one can begin to evaluate the electroencephalograms under strict technical observations:

1. Maximum at least three times the intensity (21 mm = 50 uV) which must be used in accordance with the standard of the electroencephalograph.
2. Simultaneous registration of the electrocardiogram and breathing as an additional proof of the technical efficiency of the electroencephalogram apparatus and identification of superimposed artifacts.
3. Continuous electroencephalogram diversion (lead-off) of a minimum of 20 minutes with no less than eight intensification channels in order that intermediate bioelectrical deviations (variations) are not overlooked.

Besides being inadequate the electroencephalogram so obtained may even give rise to serious error. Only the pattern of several synchronized neurologic-brain electrical findings

TABLE I

Continued Clinical-Electroencephalographic Correlation in Dissociated Brain Death with Present Heart Activity



permits a final and definitive opinion on brain death. The latter corresponds to the clinical and electroencephalogical absolute stationary appearance, because death contrary to disease has no comprehensible progress profile.

Death or Resuscitation

A functional resuscitation was observed in short-term intervals[11] after studying the brain wave in conjunction with surgery and after a successfully re-animated cardiac arrest, especially in hypothermia. Furthermore, reversible results have been noted in cases of deep anesthesia[15,24] and in poisoning with hypnotics.[11]

Isoelectrical Electroencephalogram

Table 1 shows the progressive profile of clinical-electroencephalogical findings in the four instances. It was assumed that death (Schwab) was evident at the time of the first electroencephalogram-lead as well as in the third and fourth leads during the further observations. The zero-lines do not show rhythmic down-directed variations corresponding to the action potential of the electroencephalogram.

It is clearly shown that the electroencephalogram as an indicator for the determination of brain death is of value, but only the subsequent readings determine the final diagnosis of "brain

TABLE 2

No.	Age Sex	Primary Illness or Basic Disease	Cause of Brain Damage	Length of Illness till death in hours	Length of Isometry till death in hours
1	2½ yrs	Tetanus	Asphyxia through continuous cramps before admission	72	24
2	25 yrs	Comb. mitral defect	Myocardial failure. Ischemic brain damage	36	22
3	60 yrs	Mediastinal tumor relapse	Collapse from hemorrhage	60	60
4	36 yrs	Fall from great height	Epidural hematoma. Basal skull fracture Cerebral contusion	72	48
5	16 yrs	Accident; trauma of brain. Mediastinal hemorrhage	Cerebral contusion	3	1
6	35 yrs	Accident; trauma of brain. Multiple fractures. Tearing of heart & liver	Cerebral contusion. Meningitis	312	48
7	27 yrs	Septic abortion Perforation of uterus	Cardiac arrest Cerebral anoxia	120	48
8	47 yrs	Accident; trauma of brain. Upper arm fracture	Cerebral contusion. Subdural hematoma	96	6
9	66 yrs	Arterial embolism	Subarachnoidal hemorrhage after streptokinase therapy	48	24
10	39 yrs	Mitral re-stenosis	Cerebral anoxia	12	2
11	3 mos	Multiple deformities	Stoppage of heart through respiratory insufficiency	96	29
12	33 yrs	Tuberous brain sclerosis	Anoxemic cardic arrest through convulsion (spasm)	96	48

death" as differentiated from "trance" (Scheintod). The question then arises immediately: after what time interval does a restoration of neurological and brain electrical impulses fail to appear?

Determination of Time of Death

The relatively small number of cases observed with the isoelectrical electroencephalogram and the clinical correlation of the findings do not allow a clear-cut answer as to the moment of death. We concur with other authors (Scharfetter and Schmoigal) that there is no agreement on how long an electroencephalogram must remain isoelectric before a dissociated brain death can be confirmed. Schwab proposes to wait through two 30-minute time periods; Fischgold[23] three hours, Spann, Kugler and Liebhart six hours, Jouvet more than 24 hours, and our French colleagues (Ordre National des Medicins) 48 hours; whereas Müller, Scharfetter and Schmoigl as well as Rittmeyer and Bushart leave the question open.

It would appear that a responsible decision could be made when an isoelectric electroencephalogram in conjunction with the clinical brain death exceeds four hours, because reports of isoelectric curves with successful resuscitation beyond the four-hour limit[1,3,13,18,24] fail to withstand critical analysis: either precise clinical data were not given or the electroencephalogram was not completely isometric. We doubt that a large series would prove any exception showing that after the expiration of four hours a functional recovery of brain activity occurs. Thus we believe that basically the determination of the time of death with the aid of the isometric brain current pattern must be established on a large series of cases and on uniform observation criteria, rather than on the opinion of an individual who may have made a few observations.

A corticogram or subcortical lead with the aid of deep electrodes[6,12] to confirm brain death will remain irrelevant until it has been proven that the electroencephalogram from the scalp does not resolve the problem.

Our Observations

During a study of disturbances of consciousness during surgery we noted 12 instances in which dissociated brain death was obvious as observed by continuous brain electric isometry. A total of 28 electroencephalograms were made. During the observation time the heart performance was satisfactory and the circulatory system was supported with vasoconstrictive medication. In each case continuous breathing was supported. Complicating causal factors for a disturbance of the consciousness in form of a metabolic disorder[2,7] were excluded. The clinical criteria of brain death remained unaltered, and electroencephalographic tracings demonstrated that brain activity failed to occur after isometry was established. All patients expired in spite of our efforts (Table 2).

Discussion and Summary

Successful re-animation in the past few years now requires a revision of the criteria pertaining to the time of death, which up to this time depended upon the activity of the heart and circulatory system. The brain function is now assigned a more dominating role in the decision between life and death. Furthermore, recent homologic transplantations, particularly of the heart, force us to conclude that cessation of brain function is a more logical determination of death even though the heart is pulsating.

For the diagnostic assurance of the dissociated brain death the electroencephalography as a quantitative procedure has become vitally important: the isometry in the electroencephalogram confirms the clinical diagnosis of cerebral death; but a proven wave activity negates brain death. However, this is not sufficient. We must ascertain beyond all statistical doubt with the aid of the bioelectric curve pattern the effective time interval associated with irreversible death of the brain.

Thus there should be available in the future fundamental investigations covering a large series in order to establish a definitive time limit before death can be pronounced. The single investigator cannot do this on the limited basis of his own few patients. Thus we have arranged a cooperative association with surgeons, neurosurgeons, neuropsychiatrists, and electroencephalogram-versed-neurologists to clarify conclusively the "effective time of death." We speak of "effective death time" because in a single case the precise moment of

death cannot be exactly determined. When the clinical diagnosis of brain death can be proven objectively by electroencephalography, then a declaration of death in spite of a pulsating heart will raise no objection medically.

Legal obligations and responsibility for setting the time of brain death, when the heart is still pulsating, further complicate the problem, considering the aspects of donor selection for a homologic organ transplantation. Because of an optimal short ischemic time a dead brain with intact circulation, in contrast to a cadaver brain, allows systematic transplantation and a more favorable prognosis for the recipient.

Because of the effective use of resuscitation methods and the increasing number of re-animation cases the danger arises that in hopelessly brain-damaged patients unnecessary revival efforts will be made that will not, however, improve the patient's prognosis. It must not be the goal of modern medicine to maintain decerebrated heart-lung individuals, because medical care without a chance of patient improvement is for both relatives and nursing personnel depressing and futile.

Translated by: Emil Schleicher, Ph.D.

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*Richardson Wright: Hawkers and Walkers in Early America, 1927.

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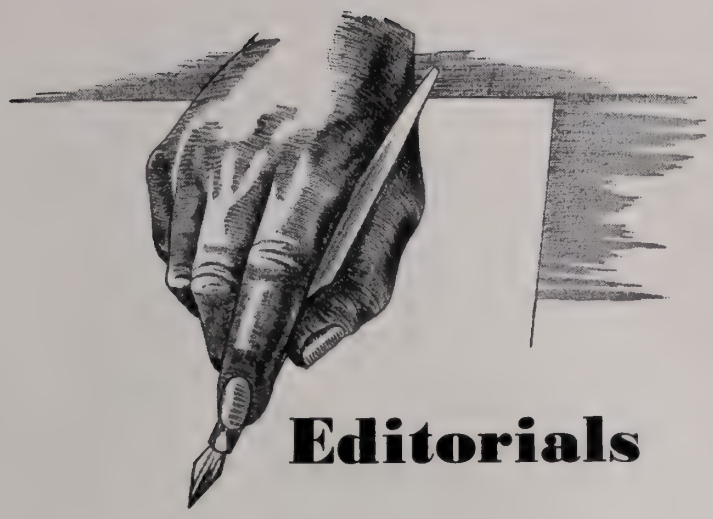
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Editorials

The Bonn University and Minnesota Medicine

THIS ISSUE OF MINNESOTA MEDICINE was contributed by the faculty of the Medical School of the University of Bonn, West Germany. During the childhood of the senior members of the Board of Editors of this journal a period of postgraduate study abroad preferably at a German language school was de rigueur for the promising young medical graduate of the United States. This custom has diminished somewhat, although physicians continue to visit in Central Europe nowadays as tourists. With this issue readers of MINNESOTA MEDICINE can learn what is going on in Bonn without making the grand tour. We thank the University of Bonn, its medical school, and particularly those members of its faculty who have contributed to make this a notable issue of MINNESOTA MEDICINE.

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Portacaval Shunt

THERE IS GENERAL agreement that portacaval anastomosis substantially reduces the risk of hemorrhage from esophageal varices in patients with cirrhosis and portal hypertension. This has been supported by the data of many investigators in both controlled and uncontrolled studies. Unfortunately, despite nearly 25 years of experience with the procedure, it is not possible to predict whether a patient can be expected to live longer with surgery than without.

In a compelling plea for "properly randomized, well-documented investigations," Grace, Muench and Chalmers[1] pointed out the lack of reliable data. They reviewed 65 papers and classified them according to the degree of control and the degree of enthusiasm for the operation. Their results indicated a striking inverse correlation between the enthusiasm of the authors and the control used in the study.

In the past few years some prospective, adequately controlled studies have been initiated, and some results are available. The results are most helpful in the case of the portacaval shunt in patients with varices but with no history of bleeding: the prophylactic shunt.

In 1965, preliminary results of a cooperative study conducted in twelve Veterans Administration Hospitals were published[2]. The investigation was prospective and randomized, and the results indicated no increase in survival over a period of up to three years when the 39 patients operated prophylactically were compared with their unoperated controls.

Conn and Lindemuth[3] published the most recent results of their prospective controlled study of the effect of prophylactic shunt on the survival of 68 cirrhotic patients. During the period of followup, up to nine years, the survival was greater in the unoperated control patients despite a greater frequency of bleeding from varices. The usefulness of prophylactic shunt in a subgroup of these patients who can be identified as undergoing greater risk of hemorrhage—those with ascites—may be of value; but the results have not as yet been published.

The data is scantier but more promising in the case of *therapeutic* portacaval shunt, in accord with the conclusions of Drs. Gütgemann and Esser in this issue of MINNESOTA MEDICINE.* The Veterans Administration cooperative group studied 39 patients who received a portacaval shunt after an initial hemorrhage from varices. After six months the survival probability was similar in the operated and control patients, and by two years the operated group showed a greater survival. Within the shunt group, the patients with hepatomegaly fared somewhat better than those without.

Certainly the available data is not conclusive, but it forms the basis for a tentative set of guidelines in the clinical management of a difficult problem. First, prophylactic surgery does not seem advisable in the unselected cirrhotic with varices, but it may prove to be of value in cases with an increased risk of bleeding, such as patients with ascites. And second, operation may prolong life, on the average, in patients who have had an episode of bleeding. Hopefully, the role of portacaval anastomosis in the therapy of the patient with esophageal varices will be clarified in the next several years.

Arnold P. Kaplan, M.D.
Minneapolis, Minnesota

*See page 1517.

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Difficulties in the Diagnosis of Hypernephroma

It has been said that "to know syphilis is to know medicine." It may be said, with equal verity, that "to know hypernephroma is to know medicine." Like syphilis, hypernephroma may mimic many diffreent diseases and deserves the title, "the great imitator." Kiely and more recently Vahlensieck and St. Gödde* have pointed out that the classic triad of loin pain, flank mass, and gross hematuria are late manifestations of the disease and are not commonly noted by the internist examining patients who eventually are proved to have a renal neoplasm.

Hypernephroma may produce a wide variety of hormonal and systemic syndromes that are unrelated to the primary growth or the development of metastasis. Thus the outstanding manifestations of hypernephroma may be such nonspecific laboratory abnormalities as anemia, elevated sedimentation rate, and increased formation of rouleaux in asymptomatic patients. On the other hand, overproduction of red blood cells in cases of hypernephroma, as a result of the production of increased amounts of erythropoietin by the kidney, may lead the clinician to consider polycythemia vera. Likewise, even in the absence of hepatic metastasis, hypernephroma may cause abnormal results of liver function tests, which may revert to normal after nephrectomy. Similarly, the chief manifestation of hypernephroma may be fever of obscure origin, polyneuropathy, hypercalcemia, amyloidosis, or such nonspecific general systemic symptoms as night sweats, fatigue, and loss of weight.

It should be pointed out that, fortunately, there are few if any internal organs that can be studied as intimately as the kidney by clinical means. Excretory urography with its refinements, retrograde pyelography, nephrotomography, selective renal angiography with and without tomography, radioactive renal scans, and cytologic study of the urine are commonly employed in establishing a diagnosis of hypernephroma. Unfortunately, however, these tests may not be ordered because of the absence of suggestive signs or symptoms.

Abnormal biochemical findings such as increased levels of urinary lactic dehydrogenase and alterations in the level of urinary alkaline phosphatase have been demonstrated. It is hoped that such studies may result in a simple accurate screening test for hypernephroma.

Laurence F. Greene, M.D.†
Rochester, Minnesota

*See page 1545.
†Mayo Clinic and Mayo Foundation: Section of Urology.

Exercise - the Heart and the Doctor Athlete

In the July issue* Dr. Bryner of the Palo Alto Clinic presented results of a nine-year retrospective study of more than 100 physicians regarding their exercise, smoking, and dietary habits as related to the incidence of coronary artery disease among them. Conceptual arguments for regular endurance exercise as a prophylactic or therapeutic aid or both were reviewed and a plea made for further studies to confirm these beliefs.

As he noted, it is difficult to average or quantitate a person's activity level. In general, people tend to continue exercise which they found pleasurable in early years. Similarly, smoking habits were established in the young through advertising and example, a trend which the medical profession now labors to defeat, armed with large natural history studies of smokers.

As we learn more about alterations of risk factors through exercise, we can more comfortably and realistically advise our patients, with or without coronary heart disease.

Thomas T. Schattenberg, M.D.
Rochester, Minnesota

*Bryner, S.: Exercise—The Heart and the Doctor Athlete. Minnesota Med 51:1011, 1968.

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Fibrinolysis, Surgery and Euglobulin Clot Lysis

Doctors S. Wuelfing and P. B. Brandau* in their studies of fibrinolytic activity during the postoperative period did not find any significantly increased fibrinolysis as measured by the euglobulin clot lysis technic. In fact, it appears that their 47 patients had very few hemorrhagic complications. This is in agreement with the observation that postoperative hemorrhages are rarely due to excessive activation of the fibrinolytic system alone.

Instead of physiologic or depressed fibrinolysis the surgeon is usually concerned that excess fibrinolysis may be responsible for hemorrhage. Generally, fibrinolysis is not an isolated event or disease process. More commonly, hemorrhagic states are due to various combinations of abnormalities of blood vessels, including the unligated vessel, platelets and blood-clotting factors. In some cases fibrinolysis contributes to the hemorrhagic disorder.

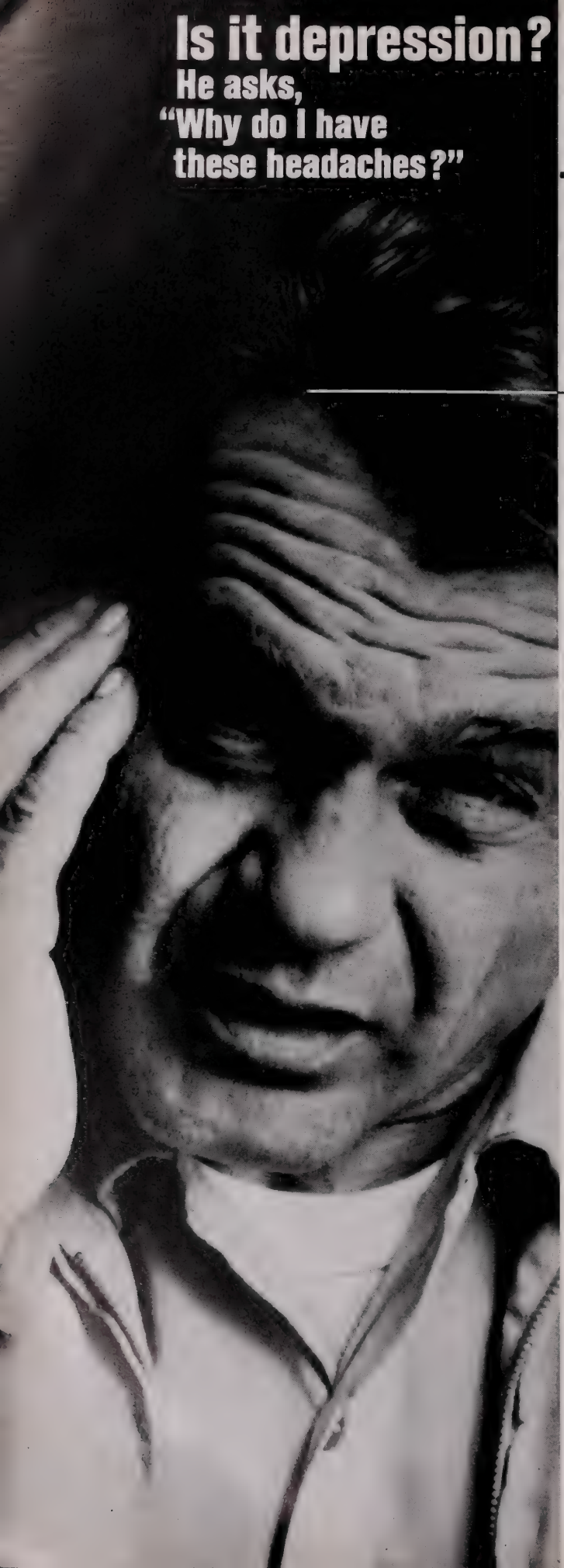
The fibrinolytic system consists of a proenzyme (plasminogen or profibrinolysin) which can be converted to a proteolytic enzyme (plasmin or fibrinolysin) by blood and tissue activators, or iatrogenically with streptokinase or urokinase. Pathologic fibrinolysis occurs when activator(s) and the subsequently generated plasmin levels exceed their respective available inhibitors. When inhibitor levels are exceeded a state of hyperplasminemia exists. Much of our information on the effects of hyperplasminemia comes from iatrogenically induced fibrinolysis with streptokinase or urokinase. The coagulation disorder that occurs in such situations is characterized by a reduced fibrinogen level, a prolonged 1-stage prothrombin time, anti-thrombin activity, decreased factor V levels, decreased platelet adhesiveness to glass, delayed clotting in fibrinogen assays, and an altered appearance to clots. With the exception of reduced factor V levels the rest of the abnormalities are due to the products of fibrinogen and fibrin proteolysis by plasmin. The proteolysis products may be thought of as circulating anticoagulants which inhibit normal fibrin polymerization, and interfere with platelet function. When plasma contains large amounts of these proteolysis products, a 1-stage protime or thrombin clot time is a rapid way of suspecting their presence. However, with the exception of iatrogenically induced fibrinollysis or the very unusual occurrence of "primary" fibrinolysis, these tests are rarely abnormal solely because of proteolysis products.

It is important to keep in mind the role played by the liver. The liver is an important second line of defense against excess activator(s) and perhaps plasmin. The normal liver appears capable of clearing activator(s) in a few minutes. The liver also participates in the clearance of proteolysis products. Unlike activator this takes several hours. A liver whose function is compromised may prolong the effects of activator and the anticoagulant effects of proteolysis products. It can be appreciated that a burst of activator triggering the conversion of plasminogen to plasmin may be missed by assay systems if clearance mechanisms are efficient.

Euglobulin Clot Lysis

The interpretation of results of the euglobulin clot lysis technic deserves special comment. The recovery of euglobulins from plasma eliminates inhibitors of activator and plasmin. The essential potential components of euglobulin are activator, plasmin, plasminogen and fibrinogen. The substrate for lysis is the patient's own fibrinogen. Fibrinogen recovery from plasma varies from 50% to 60% and plasminogen recovery from 80% to 90%. Maximum recovery of fibrinogen and plasminogen occur at different pH's. The quantity of fibrinogen lysed depends on the quantity of plasmin present either as plasmin related to hyperplasminemia *in vivo* or as a result of activator conversion of plasminogen to plasmin *in vitro*. Therefore, the ultimate clot lysis will depend on the quantity of fibrinogen and the relative concentrations of activator, plasminogen and plasmin. The test does not discriminate between activator and

*See page 1503.



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Indications: Mental depression and mild anxiety accompanying depression.

Contraindications: Glaucoma and predisposition to urinary retention. Not recommended in pregnancy.

Precautions and Side Effects: Drowsiness may occur within the first few days of therapy. Patients should be warned against driving a car or operating machinery or appliances requiring alert attention. When depression is accompanied by anxiety or agitation too severe to be controlled by ELAVIL HCl alone, a phenothiazine tranquilizer may be given concomitantly. Suicide is always a possibility in mental depression and may remain until significant remission occurs. Supervise patients closely in case they may require hospitalization or concomitant electroshock therapy. Untoward reactions have been reported after the combined use of antidepressant agents having varying modes of activity. Accordingly, consider possibility of potentiation in combined use of antidepressants. Monoamine oxidase inhibitor drugs may potentiate other drugs and such potentiation may even cause death; permit at least two weeks to elapse between administration of these agents; in such patients, initiate therapy with ELAVIL HCl cautiously with gradual increase in dosage required to obtain a satisfactory response. Caution patients about errors of judgment due to change in mood, and that the response to alcohol may be potentiated. May provoke mania or hypomania in manic-depressive patients.

Side effects include drowsiness; dizziness; nausea; excitement; hypotension; fine tremor; jitteriness; weakness; headache; heartburn; anorexia; increased perspiration; incoordination; allergic-type reactions manifested by skin rash, swelling of face and tongue, itching; numbness and tingling of limbs, including peripheral neuropathy; activation of schizophrenia which may require phenothiazine tranquilizer therapy; epileptiform seizures in chronic schizophrenics; temporary confusion, disturbed concentration or, rarely, transient visual hallucinations on high dosage; evidence of anticholinergic activity, such as tachycardia, dryness of the mouth, blurring of vision, urinary retention, constipation; paralytic ileus; jaundice; agranulocytosis.

Careful observation of all patients is recommended. The antidepressant activity may be evident within 3 or 4 days or may take as long as 30 days to develop adequately, and lack of response sometimes occurs. Response to medication will vary according to severity as well as type of depression present. Elderly patients and adolescents can often be managed on lower dosage levels.

Supplied: Tablets containing 10 mg., 25 mg., and 50 mg. amitriptyline HCl, bottles of 100 and 1000; for intramuscular use, 10-cc. vials containing per cc.: 10 mg. amitriptyline HCl, 44 mg. dextrose, and methylparaben 1.5 mg. and propylparaben 0.2 mg. added as preservatives.

For more detailed information, consult your Merck Sharp & Dohme representative or see the package circular.

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WHERE TODAY'S THEORY IS TOMORROW'S THERAP

plasmin although most clinical fibrinolytic states as measured by this test are due to activator and correlate best with other more specific assays of activator. If activator is being sought, the rapid clearance mechanisms of the liver make timing of blood sampling a critical and unpredictable undertaking. In chronic situations this is probably of less importance but may introduce unpredictable variations. The addition of epsilon-amino caproic acid to the test system, to a final concentration of 10^{-4}M, will block activator but not plasmin action. This will allow separate estimates of activator and plasmin activity in the euglobulin sample.

The use of the euglobulin lysis technic alone to study the postoperative period is insufficient. The hypothesis that there is a period of depressed fibrinolytic activity is open to other interpretations. The period of postoperative hemorrhage and/or depressed or excessive fibrinolysis will require further studies of the multiple components of the fibrinolytic system, the effect of changing fibrinogen levels due to alterations in production, factors of stress, inflammation, and interrelationships with platelet function and blood coagulation.

The impression that there is excessive fibrinolytic activity in a patient must be supported by adequate laboratory testing and cannot be left to intuition. The use of powerful drugs to block fibrinolytic activity carries the risk of depressing a physiologic activation of the clot lysis system in circumstances of excessive clot formation. This may result in massive widespread thrombosis.

William R. Swaim, M.D.*
Minneapolis, Minnesota

*Medicine and Research Service, Veteran's Administration Hospital.

Sulfobromophthalein Test

THE SULFOBROMOPHTHALEIN test is the single most valuable liver function test. It fulfills the four criteria for a good function test, namely: it effectively differentiates normal from abnormal; it distinguishes various grades of abnormality; it contributes information not already available from a simpler test; it is technically simple. In the light of its overwhelming value and considering the millions of doses of the drug which have been given, the incidence of 32 anaphylactoid reactions, including 14 fatalities, is an acceptable risk. Shafer and Gregory* in a previous issue have indicated the precautions necessary to reduce the chance of a serious reaction, namely: preparation of a possible acute anaphylactoid reaction and prohibition of this dye's use in patients with an allergic or asthmatic history.

The incidence of the less serious side reactions such as faintness, chills, injection discomfort can be decreased by diluting the drug and by slow administration over a period of five minutes. The manufacturer has insisted on putting the dye out in a concentrated convenient form at the expense of some increase in side effects. Recent work indicates that another dye, Indocyanin Green, which is used clinically for cardiac output at present, is just as valid as a hepatic function test as sulfobromophthalein and is safer. Its expense is a bar to general usage, however.

Sulfobromophthalein measures mainly circulatory factors of hepatic function. Inflammatory reaction is measured best by the zinc turbidity or the cephalin-cholesterol flocculation test. The alkaline phosphatase is the best test for regurgitation or biliary obstruction. The transaminase test is the best measure of hepatic cell necrosis. The urinary hippuric acid reaction and coproporphyrin are excretory tests which measure liver function, but these are more difficult in their administration or as a laboratory procedure. As a single test of liver function, the sulfobromophthalein ranks as the best.

Earl Hill, M.D.
Minneapolis, Minnesota

*Shafer, Rex B. and Gregory, Daniel H.: Sulfobromophthalein Syndrome-Fatal Reactions. Minnesota Med 51:911, 1968.



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Usual Children's Dose: One or two teaspoonfuls three times daily.

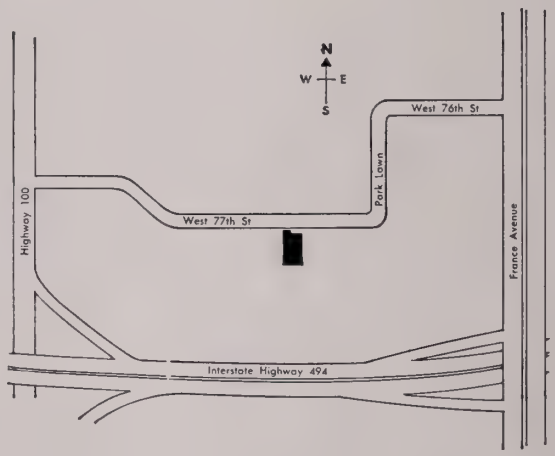
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THE RARE SYNDROME originally described in 1931 by Marinesco and collaborators[1] as a "familial disease characterized by congenital cataracts and retarded somato-neuro-psychic development" includes muscle wasting and is of a progressive nature as observed by them and later by Sjögren.[2] Drs. Alter and Kennedy present an additional patient[3] and provide further evidence of an accompanying myopathic process as evidenced by electromyographic findings and increase of serum creatinine phosphokinase. The Marinesco-Sjögren syndrome affects many tissues of ectodermal or mesodermal origin. It is inherited as an autosomal recessive disorder and probably represents an inborn error of metabolism whose exact biochemical nature remains to be determined.

M. R. Gomez, M.D.
Rochester, Minnesota

References

1. Marinesco, G., Draganesco, St., and Vasiliu, D.: Nouvelle Maladie Familiale Caractérisée par une Cataracte Congénitale et un Arrêt du Développement Somato-Neuro-Psychique. Encephale 26:97, 1931.
2. Sjögren, T.: Hereditary Congenital Spinocerebellar Ataxia Accompanied by Congenital Cataract and Oligophrenia: A Genetic and Clinical Investigation. Confin Neurol 10:293, 1950.
3. Alter, M., and Kennedy, W.: The Marinesco Sjögren Syndrome: Hereditary Cerebello-Lental Degeneration With Mental Retardation. Minnesota Med 51:901, 1968.

Test Your Word Score

Orthograde—*forward passage* (page 1497).

Decerebration—*removal of the brain* (page 1509).

Neuroleptanalgesia—*loss of sensation—due to narrowing, thinning, or fragility of the nerves* (page 1528).

Ignipuncture—*cauterization by a hot needle thrust into the tissue* (page 1533).

Exponential—*raising to a power that is to be multiplied by itself* (page 1537).

Incretory—*pertaining to internal secretion; endocrine* (page 1551)

Mentation—*mental functioning* (page 1636).

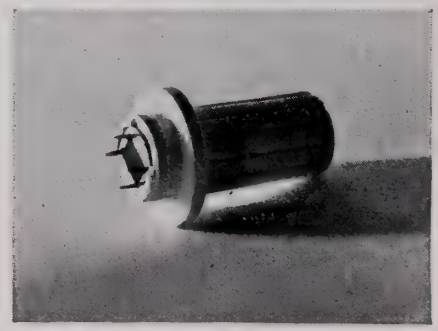
Mirabile dictu—*wonderful to relate* (page 1643).

Centipoise—*gm/cm/sec sheer rate. Water is 1* (page 1657).

Xenografts—*grafts in which host and donor are of different species* (page 1685).

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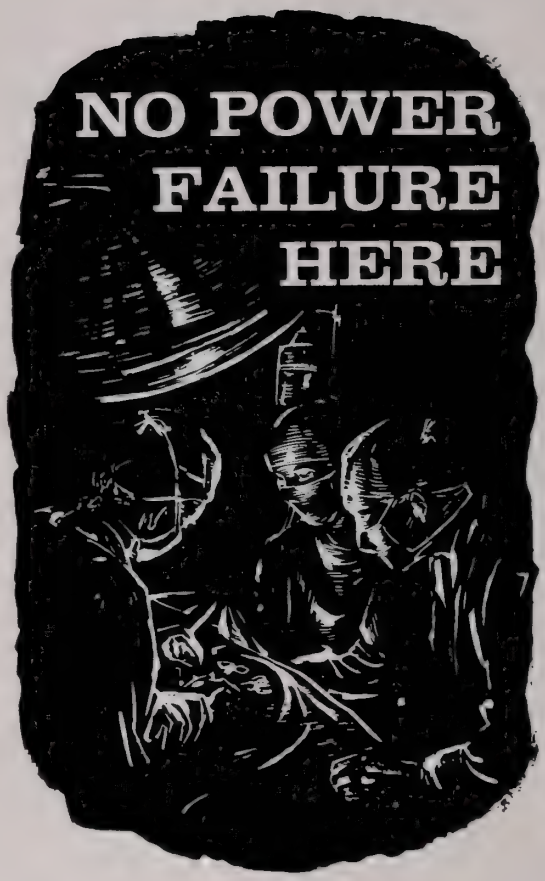
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The General Practitioner

THE ROLE of the "primary physician" of the Millis Report and the "family physician" of Dr. Caughey's report would not have inspired me to enter medicine.

Dr. Caughey tells us that the American Medical Association's ad hoc Committee believes that a "well-trained family physician with a continuing relationship with the individual patient is the best qualified person to make a comprehensive examination, guide the patient in the use of available resources and carry through a program to meet his long-term needs." But when does he find time to treat the patient? And if the role of the family physician is to insure that "there must be much more attention paid to health maintenance and preventive medicine," must he not assume the role of county nurse and social worker to the exclusion of his role as a doctor?

The general practice which I know is vital. It is an indispensable service. It is a total commitment. And in my own practice, many patients would have expired if I had been only a primary physician, for the closest specialty practice is 100 miles away.

There was the six-year-old asthmatic boy, with ruptured spleen, comatose, in shock, needing an immediate splenectomy; there was the man with high velocity deer-rifle wounds with massive hemorrhage, the woman with severe post-partum hemorrhage, requiring immediate hysterectomy. There was the man with half his frontal lobe missing, who was brought to our hospital in a sleet storm when the ambulance could not continue to the intended specialist 160 miles away. There were untold numbers of farm accidents, car accidents and acute surgical problems. These have all been cared for by me, with either a physician assistant or good nurse assistance. We have had no maternal deaths, and have had uniformly good results with a wide spectrum of general surgery and orthopedics.

The Millis Report states: "The general practitioner of revered memory . . . is vanishing . . . he leaves behind a vacuum that organized medicine has not decided how to fill."

Something is being done. Training to be a general practitioner is a lifetime endeavor; I have attended refresher courses at the Cleveland Clinic, the University of Minnesota Medical School short courses and continuation courses, plus regional and state AAGP meetings and seminars. I maintain a library of current medical books and journals.

It is my contention that 90 per cent of the patient's ills can be cared for by a well-trained, conscientious general practitioner, but organized medicine seems to be most concerned with the remaining ten per cent of obscure and complicated diseases. And it seems to me that the proposed primary physician would serve as a shuttle service rather than as a physician who treats the patient.

I believe that general practice involves total commitment of the physician, total care of the patient (often spiritual and psychological as well as medical). General practice offers for me an ideal situation in that I enjoy close proximity of home to office, hospital and church; and because no time is lost in transportation, patients are treated immediately.

General practice means freedom for greater responsibility, not diminution of it. General practice offers every opportunity for self improvement; but surgical and orthopedic training are necessary. The rather limited content of the education of a primary physician, as proposed by the Millis Report, of medicine, psychiatry, pediatrics, medical gynecology and preventive medicine can hardly encompass comprehensive care. General practice offers stimulation for self-discipline, which requires a strong faith and constant spiritual renewal.

If the recommendations of the Millis Report are adopted, I believe it will terminate rural general practice as I know it. This is not the vision of medicine which captivated me through my medical school days under beloved and revered men such as Doctors Sollman, Wiggers, Scott, Karsner, Karnosh, and Goldblatt, to mention a few. I recall with great appreciation Dr. Karnosh's commencement address October, 1943, to the Western Reserve Medical School Graduates on "The Uncommon Man"; he was in no sense speaking of the primary physician.

Lloyd H. Klefstad, M.D.
Greenbush, Minnesota

*See Editor's Soliloquy, 51:377, 1968.

Reprint from Alumni Bulletin, Second Quarter, Western Reserve School of Medicine, 1967. (Permission given)

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* anticostive, *adj.* (*anti* opposed to + *costive* causing constipation.) Against constipation. (Now isn't that a good idea in an iron-containing hematinic? We'll send you samples if you'll send a request on your Rx blank, addressed to Department 150.)

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The Editor's Soliloquy

Ein Tiger Im Tank *

A TIGER IN THE TANK, like lifting oneself by one's bootstraps, is an expression denoting the accomplishment of an exceptional and laudible feat.

This issue of MINNESOTA MEDICINE is endeavoring to start a precedent establishing international communication in medical literature. Though we live within the sphere of influence of the illustrious medical centers of the world, we are deterred by language barriers from mutual exchange of ideas. This is to our detriment; for it creates a time lag in the dissemination of many of the avant-garde ideas and achievements of eminent thinkers and doers in medical theory and practice.

True, genuine progress in any one area eventually penetrates to and is assimilated by all other areas—but only very gradually. So, with the various international exchange programs now so rapidly proliferating, we asked ourselves: Why wait for the slow diffusion of osmosis; why not initiate direct thrust and swift interchange in medical journalism as well as in other fields?

By sheer good fortune this Editor was able to make the acquaintance of an honorable, noble and far-seeing West German surgeon from the University of Bonn: Herr Professor Dr. Gütgemann, who envisioned and articulated the tremendous value accruing to the whole of medical science by establishing better and fuller international communication in medical literature. Though aware of our paucity of multi-linguality, he agreed, after the exchange of a few letters, to provide us with an entire issue of MINNESOTA MEDICINE, expounding some of the revolutionary medical advances germinating in and emanating from the valley of the Rhine.

To prepare a Special Issue of any medical journal is a task of no mean proportions: a venture that demands energy, drive, determination and authority; familiarity with a wide field of medical literature; and a keen assessment of the reading interests of subscribers.

Your Editor has had the opportunity to shake hands and visit with the author of this issue and his staff. He is proud to dedicate this issue of MINNESOTA MEDICINE to Professor Alfred Gütgemann and his able and energetic co-workers for a job singularly well done.

Carl O. Rice, M.D.
Editor-in-Chief.

*A Billboard sign frequently seen in West Germany, thanks and apologies to Shell Oil Co.

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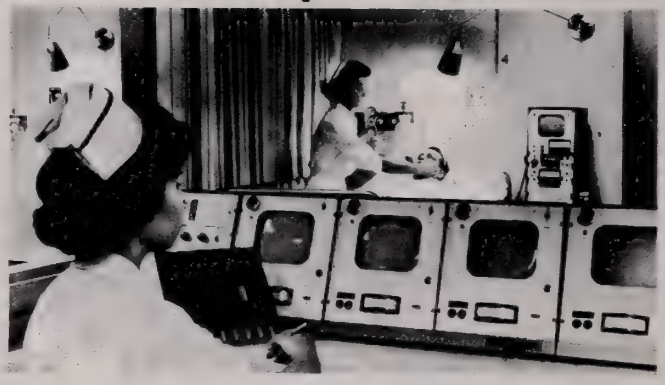
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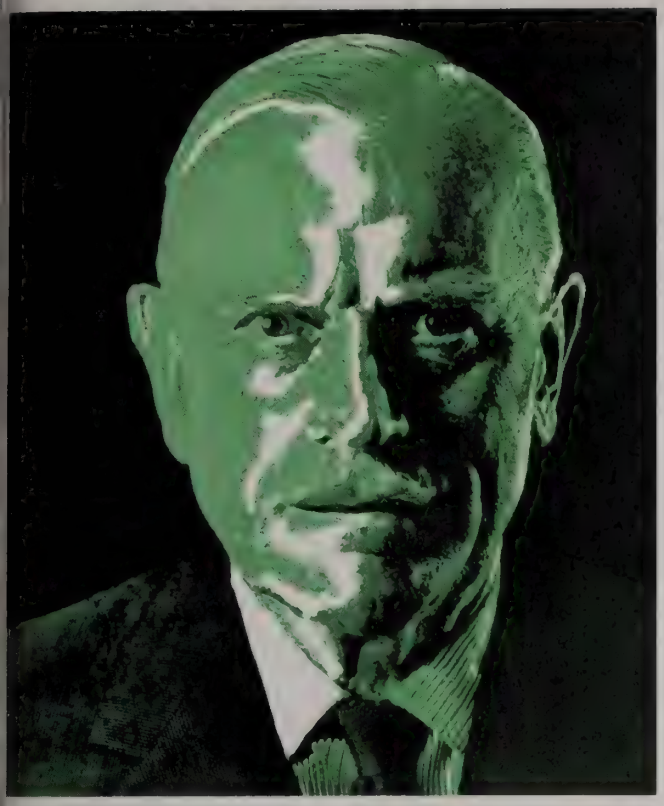
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Contraindications: Severe central nervous system depression, comatose states from any cause, hypertensive or hypotensive heart disease of extreme degree.

Warnings: Administer cautiously to patients who have previously exhibited a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) to phenothiazines. Phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides. During pregnancy, administer only when necessary.

Precautions: There have been infrequent reports of leukopenia and/or agranulocytosis and convulsive seizures. In epileptic patients, anticonvulsant medication should also be maintained. Pigmentary retinopathy may be avoided by remaining within the recommended limits of dosage. Administer cautiously to patients participating in activities requiring complete mental alertness (e.g., driving). Orthostatic hypotension is more common in females than in males. Do not use epinephrine in treating drug-induced hypotension. Daily doses in excess of 300 mg. should be used only in severe neuropsychiatric conditions.

Adverse Reactions: *Central Nervous System*—Drowsiness, especially with large doses, early in treatment; infrequently, pseudoparkinsonism and other extrapyramidal symptoms; nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache. *Autonomic Nervous System*—Dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, nasal stuffiness, and pallor. *Endocrine System*—Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema. *Skin*—Dermatitis and skin eruptions of the urticarial type, photosensitivity. *Cardiovascular System*—Changes in the terminal portion of the electrocardiogram have been observed in some patients receiving the phenothiazine tranquilizers, including Mellaril (thioridazine hydrochloride). While there is no evidence at present that these changes are in any way precursors of any significant disturbance of cardiac rhythm, several sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients previously showing electrocardiographic changes. The use of periodic electrocardiograms has been proposed but would appear to be of questionable value as a predictive device. *Other*—A single case described as parotid swelling.

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Warning: If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Instances of severe bleeding have occurred. Persistent or severe dyspepsia may indicate peptic ulcer; perform upper gastrointestinal x-ray diagnostic tests if drug is continued. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy. Use with caution in the first trimester of pregnancy and in patients with thyroid disease.

Precautions: Before prescribing, carefully select patients, avoiding those responsive to routine measures as well as contraindicated patients. Obtain a detailed history and a complete physical and laboratory examination, including a blood count. Patients should not exceed recommended dosage, should be closely supervised and should be warned to discontinue the drug and report immediately if fever, sore throat, or mouth lesions (symptoms of blood dyscrasia); sudden weight gain (water retention); skin reactions; black or tarry stools or other evidence of intestinal hemorrhage occur. Make complete blood counts at weekly intervals during early therapy and at 2-week intervals thereafter. Discontinue the drug immediately and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.

Adverse Reactions: The more common are nausea and edema. Swelling of the ankles or face may be minimized by withholding dietary salt, reduction in dosage or use of diuretics. In elderly patients and in those with hypertension the drug should be discontinued with the appearance of edema. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. The patient should be instructed to take doses immediately before or after meals or with milk to minimize gastric upset. Drug rash occasionally occurs. If it does, promptly discontinue the drug. Agranulocytosis, exfoliative dermatitis, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), or a generalized allergic reaction similar to serum sickness may occur and require permanent withdrawal of medication. Agranulocytosis can occur suddenly in spite of regular, repeated normal white counts. Stomatitis, salivary gland enlargement, vomiting, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported. While not definitely attributable to the drug, a causal relationship cannot be excluded. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, hypersensitivity angiitis, pericarditis and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.



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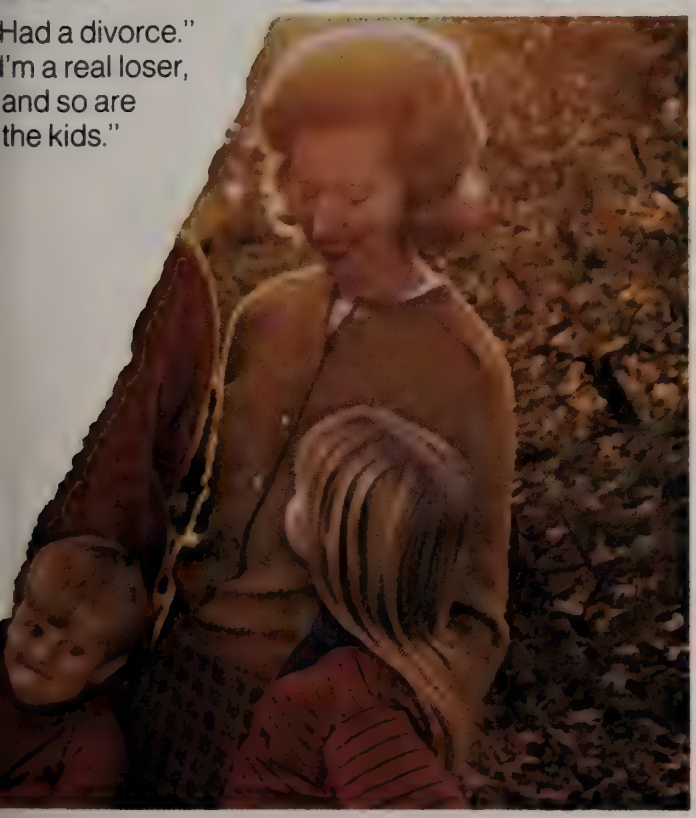
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Turn page for brief summary of Prescribing Information.

Tofrānil® imipramine hydrochloride
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Tofranil®, imipramine hydrochloride
Indications: Tofranil is recommended for the treatment of depressive states of diverse psychopathology.
Contraindications: The concomitant use of this agent and monoamine oxidase inhibiting (M.A.O.I.) compounds is contraindicated. Hyperpyretic crises or severe convulsive seizures may occur. Potentiation of adverse effects can be serious or even fatal. An interval of at least 7 days after M.A.O.I. therapy has been discontinued should be allowed before this drug may be substituted. Initial dosage should be low, increases should be gradual, and the patient's progress should be carefully observed.
Warning: Clinical reports have suggested that there may be a risk of teratogenesis associated with the use of this compound during the first trimester of pregnancy. Unless, in the opinion of the prescribing physician, the potential benefits outweigh the possible risks, it should not be used during the first trimester of pregnancy. Cardiovascular complications, including myocardial infarction and arrhythmias, have occasionally occurred in susceptible individuals. Patients with cardiovascular disease should be given the drug only under careful observation and in low dosage.
Precautions: Since suicide is always a possibility in severely depressed patients and one which may persist until significant remission occurs, such patients should be carefully supervised during early treatment. Some severely depressed patients may also require hospitalization and/or concomitant electroconvulsive therapy. Because of its anticholinergic effect, caution should be observed in prescribing the drug for patients with increased intraocular pressure.
In rare instances, transient cardiac arrhythmias have occurred in hyperthyroid patients and in patients receiving thyroid medication when this compound was added to the regimen. Imipramine may block the pharmacologic activity of guanethidine and other related adrenergic neuron-blocking agents.
The drug is not recommended at the present time in patients under 12 years of age.
Adverse Reactions: Dryness of the mouth, tachycardia, constipation, disturbances of accommodation, sweating, dizziness, weight gain, urinary frequency or retention, nausea and vomiting, peripheral neuritis, mild parkinson-like syndrome, tremors, rare cases of falling in elderly patients, confusional states (with such symptoms as hallucinations and disorientation), activation of psychosis in schizophrenics and agitation (including hypomanic and manic episodes) which may require dosage reduction and/or addition of a tranquilizer or temporary discontinuation of the drug, epileptiform seizures, orthostatic hypotension and substantial blood pressure fall in hypertensive patients, purpura, transient jaundice, bone marrow depression including agranulocytosis, sensitization and skin rash including photosensitization, eosinophilia, and mild withdrawal symptoms on sudden discontinuation after prolonged treatment with high doses. Occasional hormonal effects (impotence, decreased libido, and estrogenic effects) may be observed. Atropine-like effects may be more pronounced (e.g. paralytic ileus) in susceptible patients and in those using anticholinergic agents (including antiparkinsonism drugs).
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A lag in therapeutic response, lasting from a few days to a few weeks, should be expected. When dosage recommendations are already being followed, increasing the dosage does not normally shorten this latency period and may increase the incidence of adverse reactions.
Availability: Round tablets of 25 and 50 mg.; triangular tablets of 10 mg. for geriatric and adolescent use; and ampuls, each containing 25 mg. in 2 cc. for I.M. administration.
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TO-6757



Curbstone Consultation

RENAL HOMOGRAFT TRANSPLANT REJECTION

QUESTION: What drugs are used to prevent rejection in renal homograft transplants?

ANSWER: Only three agents when used alone have been shown experimentally to provide indefinite survival of renal homografts. These drugs are azathioprine, prednisone, and antilymphocyte serum. Azathioprine is the principal agent used for immunosuppression. Prednisone is the most valuable for securing reversal of acute rejection episodes. The effects produced by antilymphocyte serum are dependent on many variables. Whereas it may suppress early primary rejection it does not affect the cell already producing serum antibodies.

Harold D. Kletschka, M.D.
Houston, Texas

TILT TABLE

QUESTION: I recently heard about the use of a device called a "tilt table" in connection with the manned space program. Is such a device of any clinical value or is it strictly a research instrument?

ANSWER: Although the tilt table is often used as a research tool it has very definite clinical application as well. It is used to test the reflex regulatory mechanisms of such things as the heart, the brain, the vascular system, and the peripheral tissues of the body. This is accomplished through the measurement and evaluation of changes in the heart rate, the vasomotor tone, the blood pressure, and the tissue edema as a patient is changed from a horizontal to a vertical and then back to a horizontal position. It has also been described as a good test of the physical fitness of an individual. The Air Force and NASA use it as a test of the physical fitness of their pilots as well as to determine how well the pilots can undergo sudden and drastic changes in gravitational forces. Although it presently requires much experience to correctly interpret and evaluate the results, the knowledge that can thus be gained makes it a clinically important device.

Edson H. Rafferty B.S. (Biochem.)
Houston, Texas

Voice

The ideal voice for radio may be defined as having no substance, no sex, no owner, and a message of importance for every housewife.—Harry Wade

Nature to the Rescue

Common Duct Obstruction*

The gall bladder, too, has its own particular brand of magic. Mrs. Jemkins had been sick and jaundiced to a deep yellow tint for many years. All the clinics and doctors she had consulted, including myself, thought that she was dying of a malignant form of jaundice arising from a cancer of the liver or gall bladder. To operate would have been murder—or, if she had demanded it—suicide. I relieved her agony with opiates and waited for the end, which I hoped would come quickly and mercifully. She became thinner and thinner, and yellower and yellower, until she looked more like a museum mummy than a human being. To call upon her regularly would have been exploitation, and I was unable to do anything for her except prescribe pain-relieving remedies, and that could be done over the phone.

One day her husband asked me to come over to see her. It was generally believed that the end was near, and I expected to sign her death certificate at any hour. I was speechless when I saw the change in her from the week before. Her eyes had lost that deep bronze shade; she had taken a new lease on life. She said a great load had been lifted from her mind after something had happened to her abdomen. The nausea had left her; she suffered no pain. Of course I was suspicious at first that it was the advent of the anesthesia of death; many forlorn cases become hopeful and radiant just before the end. But she continued to improve, ate normally, gained weight, and finally became human once more. Fifteen years after she had been condemned to death, I saw her looking very well.

What had happened was that the obstruction in the common gall duct, which backed the bile up into the liver, was relieved by the gall bladder's boring a hole into the intestine, allowing the bile to reach the intestine by a different route. The inflammation in the gall bladder attached itself (called an "adhesion") to the nearest bit of intestine. A swelling began at the point of attachment; the swelling cut off the blood supply to the center of the inflammation, which died and sloughed through, making a perforation between gall bladder and intestine. The opening became larger as the inflammation subsided, and remained permanently. The cure was also permanent, as the pent-up secretions and poisons found a new and harmless outlet. Surgeons frequently copy Nature's technique; but we cannot do it when inflammation is present, because our patients would die of peritonitis. Nature beat us at that game.*

*Joseph A. Jerger: Doctor—Here's Your Hat, 1939.

There is as much healing power in a Beethoven sonata or a painting by Constable as in excerpts from the Bible.—George Bernard Shaw

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I think there is only one quality worse than hardness of heart and that is softness of head.—Theodore Roosevelt

The Viewing Box

Hilar Mass and Hemoptysis in a Fifteen-Year-Old Patient

THE PATIENT, a 15-year-old athlete, developed persisting cough and occasional hemoptysis about a month before admission. His general health remained good. About 10 days before admission he had clinical and x-ray evidence of pneumonia in the right lung base which cleared, but right hilar enlargement persisted. Posteroanterior chest x-ray (Figure 1) on admission showed right superior hilar shadow enlargement.

In the hospital the patient was afebrile. There was no peripheral adenopathy. Routine laboratory data were normal. Bacteriology of throat and sputum was normal. Histoplasmin skin test was positive.

Bronchoscopy showed a polypoid mass protruding from the right upper lobe bronchus obstructing that lobe and almost obstructing the right main bronchus.

Figure 2 is a coned-down bronchographic view of the carina and right main bronchus region showing a contrast-covered mass protruding into the right main bronchus from the orifice of the right upper lobe bronchus. The trachea and carina are dotted in for orientation.

A right upper lobectomy was done. The right upper lobe bronchus was completely obstructed, but the lobe was aerated apparently by collateral ventilation.

What is your diagnosis? (See next page).

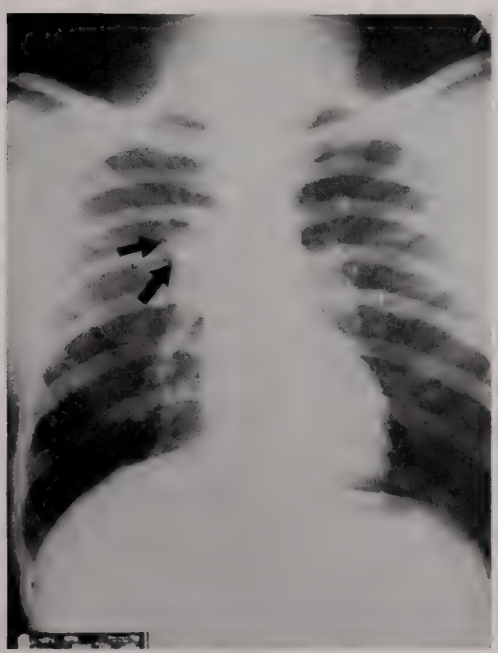


Figure 1



Figure 2

Diagnosis: The tumor was bronchial adenoma, carcinoid type, with invasion of adjacent nodes. The removed nodes also showed histoplasmosis, an unrelated coincidence.

Comment

This patient exhibited the typical clinical picture of bronchial adenoma: (1) slowly clearing or recurring pulmonary infection, (2) chronic cough, (3) hemoptysis, and (4) central pulmonary nodule or hilar mass.

Although generally an adult disease, occasional childhood cases have been reported.[1]

About 90% of the adenomas are carcinoid type histologically,[2] but the carcinoid syndrome is rare (about 2%) among pulmonary adenomas.[3,4] About half of these patients have hemoptysis, attesting to the vascularity of the tumor. Because of this vascularity, it is usually inadvisable to biopsy via the bronchoscope. This tumor has a low malignant potential, about 70% of patients of all ages surviving 10 years.[5]

William A. Wilcox, M.D.*
Warren L. Kump, M.D.*
Minneapolis, Minnesota

* Department of Radiology, North Memorial Hospital.
References may be secured from the author.

Code of Hammurabi

The total Code of Hammurabi consists of 282 sections dealing with property and persons. It is strictly a civil code, containing no religious legislation whatsoever. The paragraphs quoted here comprise the totality of the Code with reference to doctors and veterinarians.

215. If a doctor has treated a gentleman for a severe wound with a bronze lancet and has cured the man, or has opened an abscess of the eye for a gentleman with the bronze lancet and has cured the eye of the gentleman, he shall take ten shekels of silver.

216. If he (the patient) be the son of a poor man, he shall take five shekels of silver.

217. If he be a gentleman's servant, the master of the servant shall give two shekels of silver to the doctor.

218. If the doctor has treated a gentleman for a severe wound with a lancet of bronze and has caused the gentleman to die, or has opened an abscess of the eye for a gentleman with the bronze lancet, and has caused the loss of the gentleman's eye, one shall cut off his hands.

219. If a doctor has treated the severe wound of a slave of a poor man with a bronze lancet and has caused his death, he shall render slave for slave.

220. If he has opened his abscess with a bronze lancet and has made him lose his eye, he shall pay money, half his price.

221. If a doctor has cured the shattered limb of a gentleman, or has cured the diseased bowel, the patient shall give five shekels of silver to the doctor.

222. If it is the son of a poor man, he shall give three shekels of silver.

223. If a gentleman's servant, the master of the slave shall give two shekels of silver to the doctor.



Fracture Conference

Fractures of the Phalanges

Mallet Finger

Dr. Daniel Boyce:*

The first patient is a 67-year-old man who caught the distal segment of his right finger in the trigger guard of a shotgun and felt a sudden snap on extricating it. The "mallet" deformity was 10 days old when he came for treatment (Figure 1 A).

Dr. Ronald Linscheid:†

In this injury a portion of the distal phalanx has fractured into the joint and is slightly displaced. The problem is the tendency for the distal phalanx to sublux volarly and for the dorsal fragment to be pulled up by the conjoined tendon, with the result that there are late degenerative changes and "mallet" finger deformity. The options are to treat this conservatively with splintage or to perform an open reduction. We elected to insert Kirschner wires into the fragment after blocking the finger with local anesthesia (Figure 1 B). There is some tendency for the dorsal fragment to work up on the Kirschner wires; to prevent this it is helpful to put them in at slight angles. It is also difficult at times to pierce this fragment unless it is especially large. Another way to hold it is with a pull-out wire through a drill hole. If one elects to treat the fracture with Kirschner wires, it helps to take a roentgenogram within a couple of days to be sure the fracture is not becoming displaced.

Epiphyseal Fracture

Dr. Boyce:

The next patient is a 27-year-old woman who was a backseat passenger when involved in an automobile accident. She raised her right hand in an effort to protect herself and sustained an injury to the little finger (Figure 2).

Dr. Linscheid:

This fracture is just above the flare of the base of the proximal phalanx

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Conference held at the Mayo Clinic, Rochester, March 11, 1968.

*Resident in Orthopedic Surgery, Mayo Graduate School of Medicine (University of Minnesota), Rochester.

†Assistant Professor of Orthopedic Surgery, Mayo Graduate School of Medicine (University of Minnesota) and Consultant, Section of Orthopedic Surgery, Mayo Clinic, Rochester.

of the little finger and is deviated ulnarly and dorsally. It is analogous to the fractures seen in children that are type II epiphyseal injuries, in which the finger is also in ulnar deviation and is dorsally displaced. The reason we elected to show this method of treatment with the use of a flexed aluminum splint incorporated in a gauntlet cast is that the splint is not bent enough. The finger was in only slight flexion. The splint should be bent back on itself so that the immobilized fingertip is pointing at the tuberosity of the scaphoid.

Dr. Richard S. Bryan:*

In the epiphyseal fractures in this area in young children, a ballpoint pen fits nicely into the web space between the metacarpal heads, and the fracture can be reduced with minimal force by squeezing the fingers together. It's a

*Consultant, Section of Orthopedic Surgery, Mayo Clinic, Rochester.

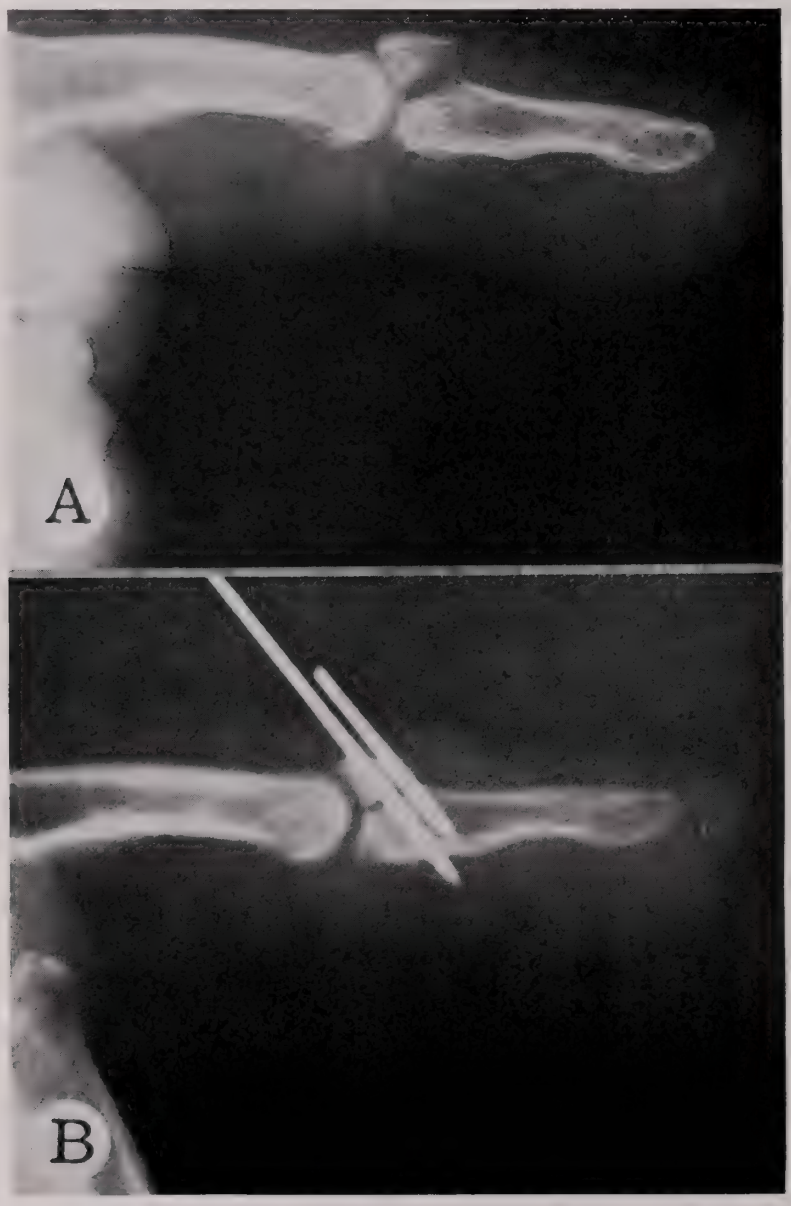


Fig. 1 *(A)*—Intra-articular avulsion fracture of distal phalanx associated with "mallet" finger. *(B)* Fixation with Kirschner wires.

neat trick.

Dr. Mark B. Coventry:*

How would you prefer to immobilize such a fracture once it has been reduced?

Dr. Linscheid:

I think it is difficult to hold because it tends to return into ulnar deviation. I have been using a gauntlet cast with an aluminum (Alumnafoam) splint.

Dr. Bryan:

What would be wrong with taping this finger to the ring finger and allowing the ring finger to act as a mobile splint?

Dr. Linscheid:

That should be quite satisfactory for this fracture.

Dr. Boyce:

The next case is that of an eight-year-old boy who injured his long finger.

Dr. Linscheid:

We didn't know how he injured his finger, but the deformity was obvious (Figure 3). There is a proximal phalangeal fracture with volar angulation at the fracture site (Figure 4-A). Is this a typical position for this fracture to assume?

Dr. Sherwin Goldman:†

It seems it would occur the other way, the flexors being stronger.

Dr. Linscheid:

The flexors are stronger. Can you think of any other reason why a typical deformity might occur in this direction rather than be dorsally angulated?

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†Resident in Orthopedic Surgery, Mayo Graduate School of Medicine (University of Minnesota), Rochester.

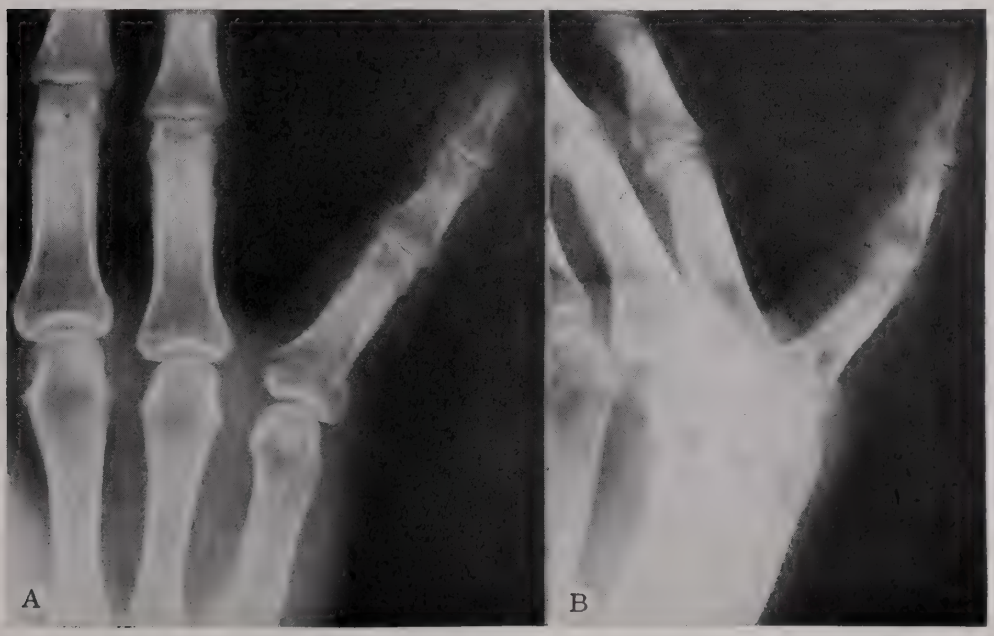


Fig. 2 *(A)*—Anteroposterior view of fracture of proximal phalanx of fifth finger, showing ulnar deviation at fracture site. *(B)* Lateral view demonstrates dorsal angulation at fracture site.

Dr. Goldman:

The extensor hood, particularly the pull of the lumbrical muscles.

Dr. Linscheid:

The extensor hood forms a sling over this area of the proximal phalanx. The wing tendons and the lateral bands come up in an oblique direction and connect with the central slip through oblique fibers. The flexor superficialis attaches at the proximal third of the middle phalanx so that, although the flexors are stronger than the extensors, because of the interposed joint and the anatomy of the extensor apparatus this is the typical deformity for a

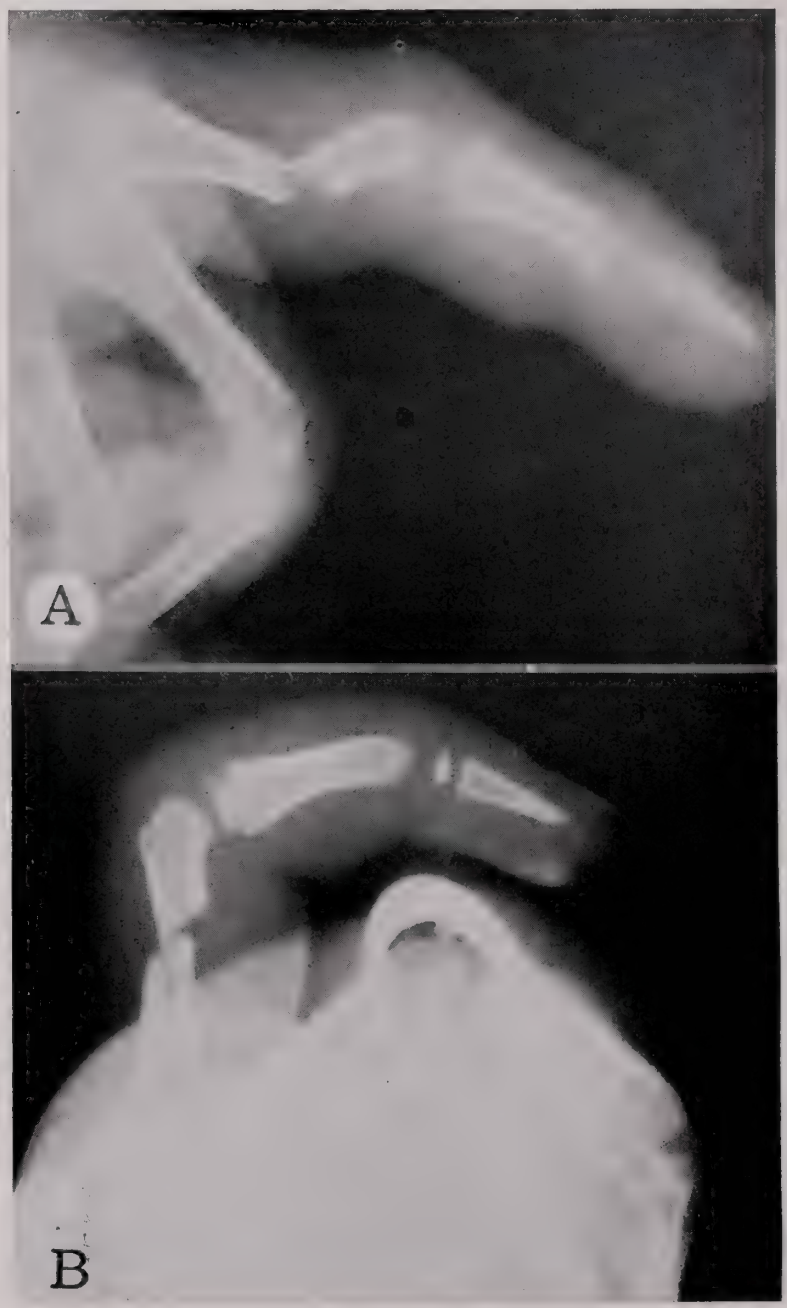


Fig. 3 *(A)*—Fracture of proximal phalanx of right index finger, showing typical deformity. *(B)* Postoperative reduction held by aluminum splint. There is not enough curve of finger and joint to maintain reduction.

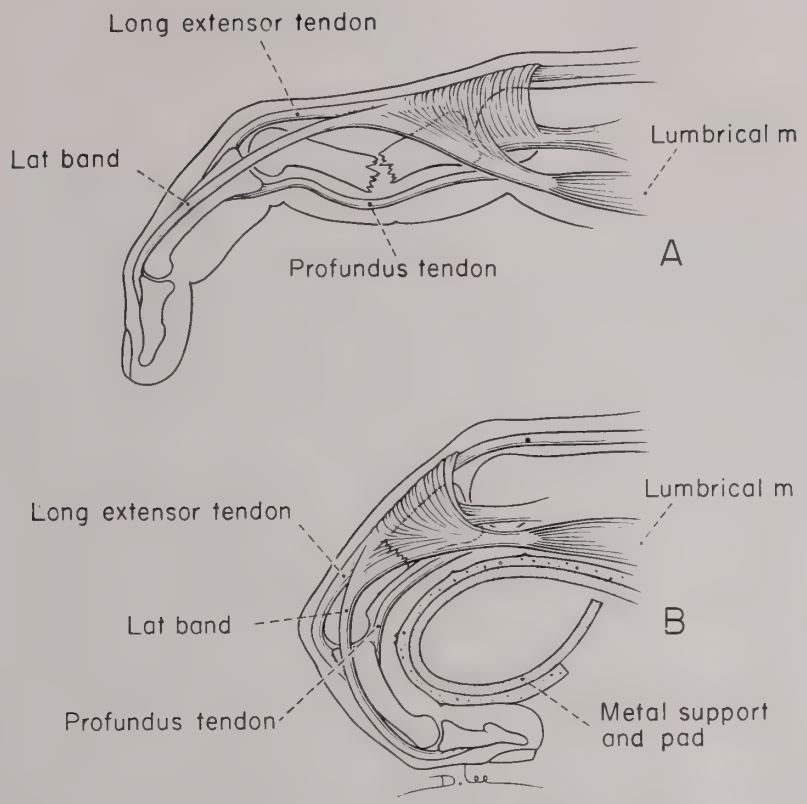


Fig. 4 *(A)*—Demonstration of typical deformity of proximal phalangeal fracture and part played in its production by extensor mechanism. *(B)* Reduction over a splint balances deforming forces.

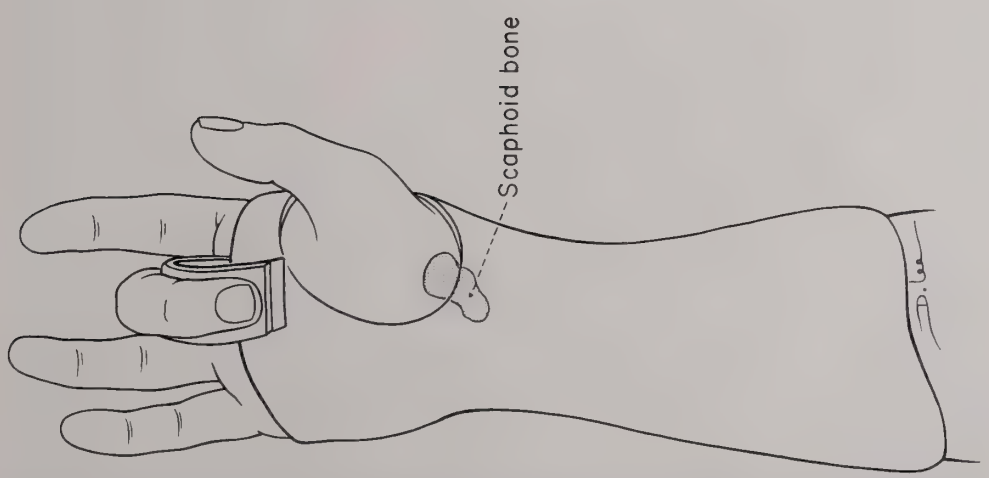


Fig. 5—Demonstration of flexed finger pointing to tubercle of scaphoid on a modified Böhler splint. Normally all fingers point to tubercle of scaphoid when flexed. Nail bed should lie in same plane as adjacent fingers when flexed to control rotation.

fracture of the proximal phalanx. How are you going to treat this?

Dr. Goldman:

Reduce it by manipulation under adequate anesthesia and immobilize it in flexion.

Dr. Linscheid:

Roughly flexion of 40° at the metacarpophalangeal joint, 80° at the proximal interphalangeal joint, and 30° at the distal interphalangeal joint would be usual. The finger would be well curved around a splint device. Do you have to worry about rotation in this fracture, and if so, how would you align it?

Dr. Goldman:

It depends on the type of immobilization used. It is quite difficult with a cast on the fingers. A splint may be twisted to align the finger.

Dr. Linscheid:

Basically you are describing the Böhler type of immobilization. This involves a gauntlet cast with a volar splint on the finger, which is acutely curved. The point to be made here is that one cannot align rotation of the finger unless it is flexed sufficiently to cause the pulp of the finger to face proximally along the forearm. The finger should point toward the tuberosity of the scaphoid (Figure 5). This controls alignment. But to control rotation the nail of the injured finger should lie in the plane of the adjacent fingers. If one tries to control rotation of the finger with the finger only slightly flexed, one has no idea whether or not the finger is going to point toward the scaphoid with full flexion after it has healed. The most common mistake made in the treatment of this type of fracture in the emergency room is not to bend the splint into a tight, closed loop; thus the finger is not held in enough flexion (Figure 4 B). The finger should be pointing in a proximal direction when lying reduced on the splint.

Dr. Paul R. Lipscomb:*

It should be emphasized that this fracture requires anesthesia and manipulation for reduction, before it is put over a splint.

Dr. Linscheid:

A good point. It does take anesthesia by injection into the fracture site or by metacarpal block.

Dr. Richard N. Stauffer:†

Is there any place for pulp traction in this kind of fracture?

Dr. Linscheid:

I haven't found it necessary to use pulp or phalangeal traction; however, it would depend to some extent on how badly the phalanx is fractured and how stable the fracture is. Most of the time, a narrow tape over the fingernail, attaching it to the splint (Figure 5), is sufficient. An alternative is demonstrated in the next case.

Compound Fracture

Dr. Boyce:

A 57-year-old man had a truck jack fall on his right index finger. Exami-

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nation at the emergency room disclosed a 5-cm irregular volar laceration and crushing of the skin. The laceration extended into the tendon sheath and exposed the neurovascular bundle (Figures 6 A and B).

Dr. Linscheid:

This represents the same type of injury—essentially a transverse fracture of the proximal phalanx with volar angulation at the fracture site. Here we have a compounding wound with the skin rather abraded, and a laceration that exposes the nerve and vessel. Inspection of the depths of the wound



Fig. 6—*(A)* and *(B)*, Fracture of proximal phalanx of right index finger. *(C)* and *(D)*, Postoperative reduction with crossed Kirschner fixation.

showed that the flexor sheath was stripped off in part, but that the flexor tendons were intact and seemed to be in good condition. How do we treat this wound? Obviously we have to use the same type of wound treatment for a compounding fracture here that we would use in other areas. It must be thoroughly cleaned and debrided of dead or necrotic tissue or any tissue that is irretrievably soiled. We have the added problem of how to maintain the gliding property of these tendons when healing has been completed. This patient was taken to the operating room and the wound was thoroughly cleaned. The neurovascular bundle was protected and the loose fragments of flexor sheath were sharply excised, with exposure of the tendons at the depth of the wound. A tiny pack was inserted into the wound to allow drainage. What happens if we treat this fracture on a Böhler splint and apply pressure under the volar aspect of the finger? We force the flexor tendons against the injured periosteum at the fracture site and increase the chances of having tendinous adhesions. In this situation there is good indication for internal fixation with crossed Kirschner wires (Figures 6 C and D). The finger was easily reduced and the wires were fairly easily inserted percutaneously. The alignment of the finger was checked, the finger being flexed to be sure the pulp was pointing toward the tuberosity. The wound was packed open for 24 hours and then closed with adhesive tape (Steri-strips). Daily motion in the two distal joints to prevent tendinous adhesions was encouraged.

Dr. Lipscomb:

I think I would agree with you. This would be one instance in which one would not want to put the finger in acute flexion and push the structures further in contact with the bone.

Dr. Linscheid:

To summarize, let me make the following points: (1) Rotation as well as alignment of the fragments must be considered in the reduction of phalangeal fractures. (2) If joint surfaces are involved, open reduction and Kirschner wire fixation even in these small finger joints should be considered to effect accurate reduction. (3) The compounding hand injuries still require adequate wound care before the fracture can be treated definitively. (4) Only the injured part should be immobilized, to prevent hand stiffness.

Ronald L. Linscheid, M.D.*
Daniel Boyce, M.D.*
Einer W. Johnson, Jr., M.D.*
Rochester, Minnesota

*Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

The Progress Notes of Hippocrates

The young man who was lodged by the Liars' Market* was seized with fever from fatigue, labor, and running out of season. On the first day, the bowels disordered, with bilious, thin, and copious dejections; urine thin and blackish; had no sleep; was thirsty. On the second all the symptoms were exacerbated; dejections more copious and unseasonable; he had no sleep; disorder of the intellect; slight sweat. On the third day, restless, thirst, nausea, much tossing about, bewilderment, delirium; extremities livid and cold; softish distention of the hypochondrium on both sides. On the fourth, did not sleep; still worse. On the seventh he died. He was about twenty years of age.†

*Liars' Market—probably a district or neighborhood in Athens.
†Hippocrates.
What's Your Diagnosis?
Diagnostic Possibilities: This might have been an acute heavy metal poisoning; acute parasitic disease; kala-azar, porphyrinuria.

The Physician's Workshop

Side-to-Side Anastomosis of the Small Intestine*

Using Russian Suture Apparatus

A. BLOMER, M.D.*
N. DRAZNIN, M.D.*
U. ROSSECK, M.D.*
Bonn, West Germany

THROUGHOUT THE years a number of surgical suturing machines have been developed. Most of them are based on the stapling principle.

Several instruments designed for thoracic, abdominal and vascular surgery have emanated from the Moscow Institute of Surgical Apparatus and Instruments.[1] Von Petz,[4] in 1924, supplied a method of a reliable, speedy, aseptic, and bloodless closure with his gastrointestinal suturing apparatus.

We evaluated experimentally[2,3] the Russian models† for side-to-side small intestinal anastomoses and an instrument‡ (Figure 1) which is designed for mechanical suturing of the hilum of the lung, and may also be used for bowel closure. Similar to the apparatus of von Petz and Friedrich, a double row of vitallium staples is inserted. After transection of the mesentery the bowel is fixed between the two branches of the clamp by means of a wing nut. A plunger which is activated by pressing on a lateral lever drives first the U-shaped metal clips through the anterior and posterior bowel wall and then bends them into a B-shape.

The apparatus for side-to-side gastroduodenal anastomoses§ (Figure 2) consists of two branches and a plunger with cutting edges. The branches are loaded with two rows of clips which are inserted into the two intestinal lumina through stab wounds and then united. The cutting plunger is then advanced and creates at once a stoma and one-layer anterior and posterior suture lines. The stab wounds are closed with inverting No. 3-O silk sutures.

The Procedure

The operation was performed aseptically under nembutal anesthesia on 12 dogs weighing from 10 to 15 kilograms through an upper mid-line incision. A jejunal loop was isolated by transecting the mesentery for a distance of about 15 cm. Two parallel rows of staples

*From the Department of Surgery, University of Bonn. Director: Professor Dr. A. Gütgemann, Division of Experimental Surgery.

†UKL-60 and NZKA-60
‡Model UKL-60
§NZKA-60

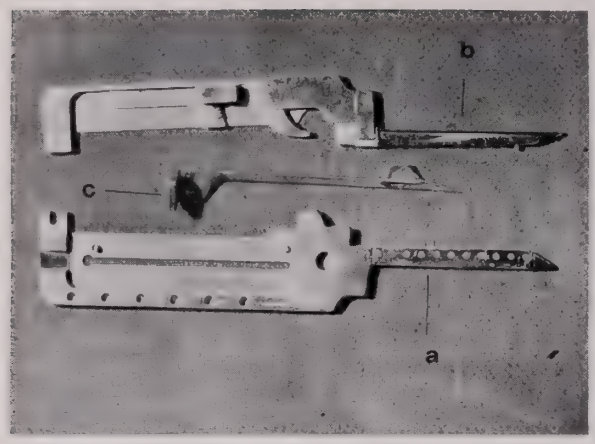


Fig. 1—Apparatus NZKA-60 for side-to-side gastrointestinal anastomoses: (a) Branch with double row of clip compartments. (b) Branch with lay-on surface. (c) Plunger with cutting edge.

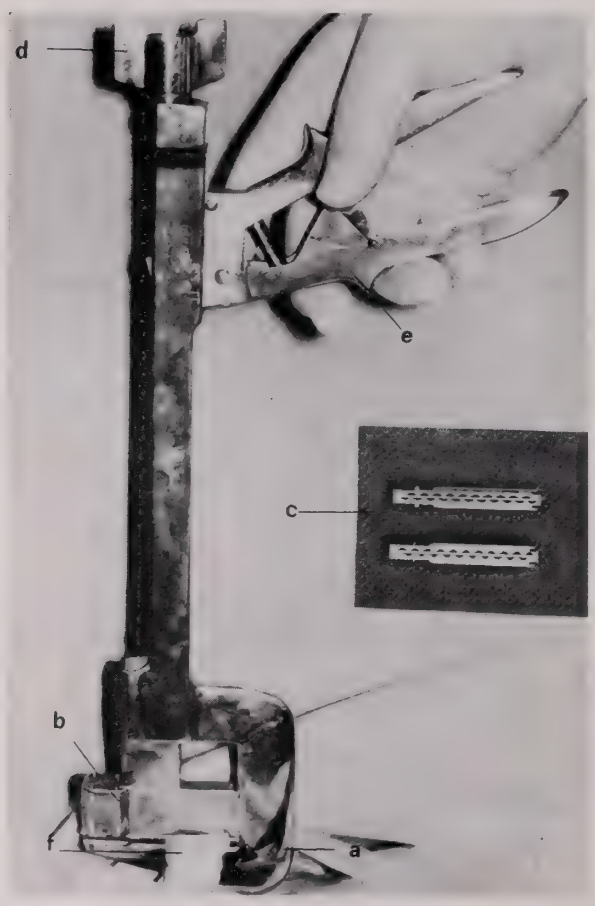


Fig. 2—Apparatus UKL-60 for suturing of pulmonary hilum: (a) Lay-on branch. (b) Clip-branch. (c) Clip container. (d) Nut for apposition of both branches. (e) Activating lever for plunger. (f) Small intestine.

were then applied with the model UKL-60. After excision of the loop both intestinal stumps were additionally inverted with interrupted No. 3 silk sutures. An isoperistaltic anastomosis between the two bowel ends was then done with the model NZKA-60, with simultaneous creation of a stoma. The anterior and posterior rows of clips were additionally secured by rows of seromuscular sutures. On the first two postoperative days the dogs received 500 ml 5.25% glucose and 500 ml of 0.9% normal saline daily. They were fed a semi-liquid diet from the third to the fifth day and solid foods thereafter.

The Observations

The time of sacrifice was varied so as to provide histological examination from the first to the eighth postoperative week. There was one anesthetic death. Eleven dogs survived.

Morbidity

Two dogs had one tarry stool postoperatively. There was no clinical evidence of suture insufficiency in any of the animals. Neither was there radiographic evidence of suture insufficiency of the intestinal stumps in any of the dogs.

Gastrointestinal X-ray examinations with barium were performed under nembutal anesthesia on the sixth postoperative day. There was free passage in all anastomoses. Disturbed bowel motility was found on occasion. However, this was probably due to deep anesthesia rather than a consequence of the operation, since it was present in the entire gastrointestinal tract. Figure 3 showing the open specimen indicates a sufficiently wide anastomosis which can be seen as a fine tissue line.

Microscopic Findings

The microscopic specimens were fixed and imbedded after removal of the metal clips and stained with hematoxylin and eosin and with van Gieson stain. The histological examinations (Figure 4) were of special interest, since they provided a simultaneous comparison of metal clip- and silk-closure. We found remaining silk sutures especially in the submucosa and muscularis propria, surrounded by

chronic granulating, fibrous tissue and foreign body reaction. There were many multinucleated giant cells and larger accumulations of granulocytes resembling abscesses. There was no foreign body reaction in the mucosa. Occasionally we saw a chronic inflammatory infiltration in the mucosa, as it is frequently seen in normal dogs. There was only a mild chronic cicatricial reaction surrounding the empty spaces created by removal of the metal clips.

The Russian suturing apparatus NZKA-60 permits not only the side-to-side small bowel anastomosis but also a side-to-side anastomosis of gastrointestinal tract and colon. We have proved in an earlier experimental series[3] that in using three different Russian suturing apparatuses, a Billroth-I- or Billroth-II-gastrectomy could be done in a reliable way as well as a side-to-side gastroenterostomy and a jejuno-jejunostomy of Braun. The advantages of a mechanical anastomosis are the exact adaptation of the layers and the exact placement of the stoma. Experience and skill on the part of the operating surgeon are not important with this technique.



Fig. 3—Isoperistaltic small intestinal anastomosis, side-to-side, opened, seven weeks postop.

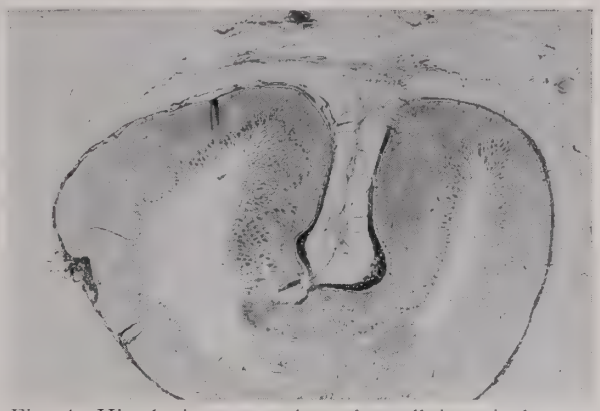


Fig. 4—Histologic preparation of small intestinal anastomosis, six weeks postop.

Summary

Side-to-side small intestinal anastomoses were performed on 12 dogs with the Russian apparatus designed for either gastrointestinal anastomosis or closure of the pulmonary hilum.

The reliability of the mechanical small intestinal anastomosis, as judged by clinical course, X-ray examination and histological findings, was demonstrated.

Translated by: H. W. Heupel, M.D., Ph.D.

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The Physician's Role

The need for access to the patient and the protective devices which are erected to contain its threat can lead to strains in the doctor-patient relationship. In some ways it is easier for the physician to fill his role if he perceives the patient more as a case than as a person; yet the impersonal approach often runs counter to the emphasis on disease as affecting the whole person and on treating the psyche as well as the soma, and counter to deep psychological needs for love and affection on the part of both the doctor and the patient. This theoretical dilemma has not yet been satisfactorily solved in medical practice.*

*King, S. H. in Richard Magraw: Ferment in Medicine, 1966.

Every new idea has something of the pain and peril of childbirth about it.—Samuel Butler

My Political Creed

I am a free citizen in a free nation.

Whoever diminishes my freedom as an individual diminishes the sum total of freedom in my country.

I am also a physician, free thus far to treat my patients to the best of my ability.

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These things being true, I cannot--I will not--stand idly by when these hard-won freedoms are under attack.

For I believe that the values upon which this country was founded are immutable and have not been eroded by the passage of years.

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Clinical Path Conference

Coarctation of Aorta as Part of Shone Syndrome*

Dr. George R. Noren:†

A male infant was born to a 20-year-old primagravida with no history of prenatal complications. The one-minute Apgar was three; at 10 minutes it was 10. Initial physical examination revealed no abnormalities. The weight of the infant was 2900 grams. On the second day of life, a grade II/VI ejection systolic murmur was heard along the left lower sternal border and the femoral pulses were thought to be weak. The pulmonary second sound was greatly accentuated. Simultaneous blood pressures were then done. The left and right arms flushed at 120 mm. Hg. and the legs at 40 mm. Hg. No cyanosis was noted. An electrocardiogram obtained at that time revealed right ventricular hypertrophy. Thoracic roentgenograms demonstrated questionable right basilar pneumonia. The overall cardiovascular silhouette was within normal limits. The infant fed slowly but gained weight consistently. He did not demonstrate any evidence of cardiac failure and was discharged at two and a half weeks of age.

The infant was admitted for the second time when three months old. The history was that for two weeks there had been slow feeding and inadequate gain in weight. Physical examination revealed abnormalities of the cardiovascular system. The point of maximum cardiac impulse was felt at the anterior axillary line in the fourth left intercostal space. A grade III/VI systolic ejection murmur was present. It was loudest along the left sternal border and radiated to the left axilla and left shoulder and posteriorly along the spine. The second cardiac sound in the pulmonary area was accentuated. The edge of the liver was palpated 2 cm. below the right costal margin. The femoral pulses were faintly palpable bilaterally and there were bounding brachial and carotid pulses. By the flush method the

*This study was supported by Public Health Service Research Grant 5 RO1 HE05694 and Research Training Grant 2 T1 HE05570 from the National Heart Institute.

†Associate Professor, Department of Pediatrics, University of Minnesota, Minneapolis; Assistant Chief, Department of Pediatrics, Hennepin County General Hospital, Minneapolis.

blood pressure in the right arm was 125 mm. Hg. and in the leg, 80 mm. Hg. The electrocardiogram demonstrated severe right ventricular hypertrophy, as in the first admission.

Over the next several days it was decided that borderline congestive heart failure was present and the patient was digitalized on the basis of 0.07~~0.7~~ mg. Lanoxin per kilogram of body weight. Following digitalization the condition of the infant improved and he was discharged one week after the second admission.

The infant was then followed in the Pediatric Cardiology Clinic and gained weight very slowly. At age six months, the blood pressure in the arms was noted to be 150 mm. Hg., respirations 90 per minute and pulse 150 per minute. The weight at that time was 12 pounds. There was a grade III/VI loud systolic ejection murmur heard best along the left sternal border. The murmur radiated well to the left axilla and back. There was a loud pulmonic second sound with questionable splitting. The liver was palpated 3 to 4 cm. below the right costal margin. An electrocardiogram revealed an axis of 85 degrees with probable left atrial enlargement. Signs of severe right ventricular hypertrophy and probable left ventricular hypertrophy were apparent. A thoracic roentgenogram showed left ventricular predominance and pulmonary vascular congestion.

A retrograde aortogram was then performed from the right brachial artery and the patient was transferred to the surgical department because of increasing cardiac decompensation.

Following an operation which was uneventful the respiratory rate was 62 per minute with retractions and expiratory grunting. The respiratory rate continued to increase with evidence of increasing congestive heart failure. Moist rales were heard over both lung fields. Immediately after operation, the blood pressure in an arm was 130 mm. Hg. and in the legs, 130 mm. Hg. The levels of electrolytes in the blood were all within normal limits with the exception that, postoperatively, the level for SGOT was 250 units. Despite intensive medical measures, the infant's course deteriorated and death occurred 24 hours after operation.

Dr. Gary E. Gathman:*

This six-month-old infant was born to a 20-year-old primagravida after an uncomplicated pregnancy. His birth weight was 2900 grams, which would indicate that he was probably a term infant, although his weight is near the lower limits of normal. Prematurity both by birth weight and gestational age, is approximately two and a half times more frequent in children with congenital heart disease than in those with normal hearts.

The patient was a male, which statistically would increase his chances of having aortic stenosis, tetralogy of Fallot, transposition of the great vessels, and/or coarctation of the aorta. Various authors have reported that the incidence of coarctation is two to four times greater in males than in females. He was quite depressed one minute after birth, which could significantly increase his perinatal mortality; however, the situation improved and at ten minutes his Apgar score was 10. The initial physical examination was normal, but one must wonder whether or not accurate evaluation of the femoral pulses was made.

On the second day of life a grade II/VI ejection systolic murmur was

*Assistant Professor, Department of Pediatrics, University of Minnesota, Minneapolis.

heard along the left lower sternal border and the femoral pulses were felt to be weak. Simultaneous blood pressures were then obtained; the left and right arms flushed at 120 mm., the legs at 40 mm. No cyanosis was present then, and apparently none was present at any time until shortly before his demise. An electrocardiogram revealed right axis deviation, a suggestion of right atrial hypertrophy, and rather marked right ventricular hypertrophy (Figure 1). A thoracic roentgenogram demonstrated a normal-sized heart with questionable basilar pneumonia. At this time the clinical and laboratory findings are quite consistent with a diagnosis of coarctation of the aorta. With the absence of differential cyanosis and equal blood pressures in both arms, the coarctation is distal to the ligamentum arteriosum. Neither subclavian artery is stenotic nor does either rise below the level of coarctation. The absence of cyanosis rules out aortic atresia or interruption of the aortic arch with the distal aortic supply coming from a patent ductus arteriosus.

Conservative medical management was adopted as the treatment of choice. The infant fed slowly but gained weight consistently and did not demonstrate any evidence of congestive heart failure. Coarctation of the aorta is the most frequent cause of congestive heart failure in the first week of life. He was discharged at two and a half weeks of age but was readmitted at three months of age because of a two-week history of slow feeding and poor gain in weight. This history is unusual for a simple severe coarctation in infancy. Generally, these infants are in trouble before three months of age.

Physical examination at this time was unremarkable except for the heart

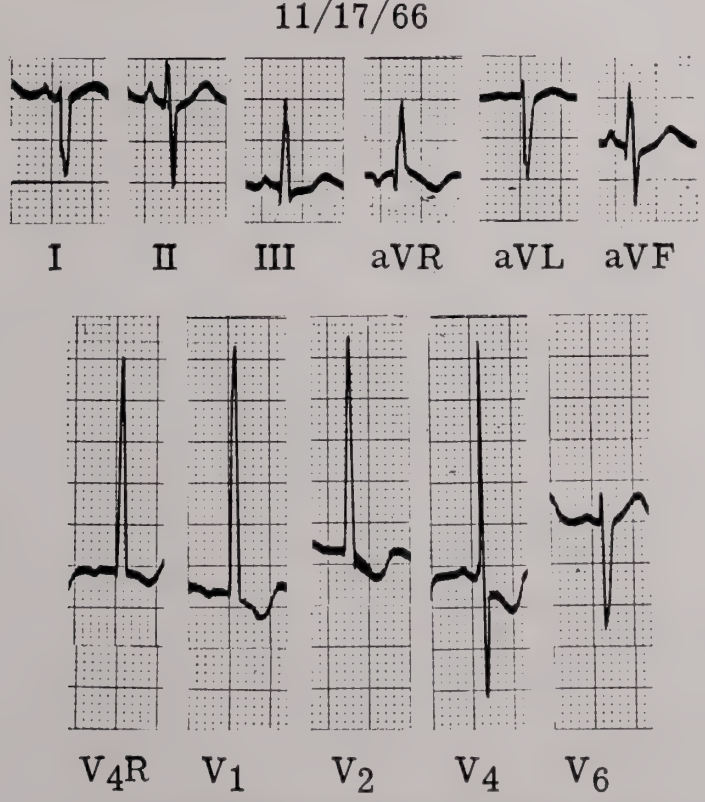


Fig. 1—Electrocardiogram made in the newborn period.

which was enlarged to the anterior axillary line in the fourth intercostal space. A grade III/VI ejection systolic murmur was heard loudest along the left sternal border with radiation to the axilla and left shoulder and along the spine posteriorly. The second heart sound, and presumably this was the pulmonic component of the second heart sound, was again accentuated. The liver was palpated 2 cm. below the right costal margin. The femoral pulses were faint and there were bounding brachial and carotid pulses. Blood pressure by flush method in the right arm was 120 mm. and 80 mm. in the legs. Because of clinical suggestion of borderline congestive heart failure, the patient was digitalized with an adequate dose of Lanoxin (0.07 mgm. per kgm.). He improved and was discharged. Delicate medical management was then continued as the treatment of choice for an infant with coarctation.

At six months of age the child was clearly in trouble again with tachycardia, tachypnea, and hypertension. His weight had leveled off to well below the third percentile for his age. Again a grade III/VI loud systolic murmur was heard along the left sternal border radiating well to the axilla and back with a loud pulmonic second sound but again with questionable splitting. The liver was palpated 3 to 4 cm. below the right costal margin. The electrocardiogram at six months of age is markedly abnormal (Figure 2). There is severe right ventricular hypertrophy with a QRS axis of about 90 degrees. This axis is further to the left than one might expect in a child with this degree of right ventricular hypertrophy. The P and T wave axes are about 60 degrees. The T waves are not diagnostic of strain, although there is some slight ST segment depression probably secondary to digitalis. The PR interval of .12 sec. is normal for this age and heart

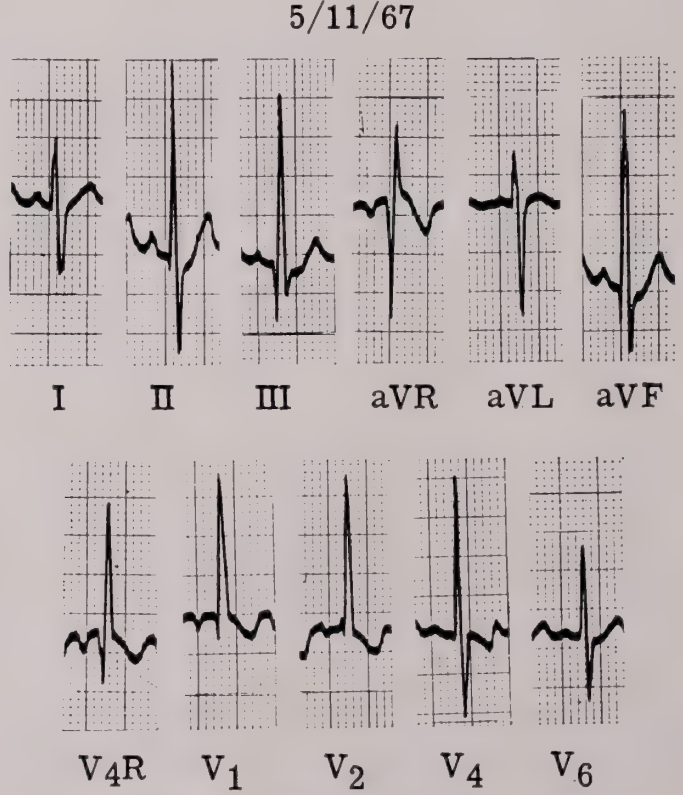


Fig. 2—Electrocardiogram made at the age of six months.

rate. The QT interval of .28 sec. with a QT_c of .45 sec. is abnormally long and is suggestive of strain. The QRS interval of 0.08 sec. is somewhat prolonged and suggests a right ventricular conduction delay, quite possibly on the basis of right ventricular hypertrophy. There are deep T waves in Leads III and aVF associated with tall R waves in Lead aVF, features which point to left ventricular hypertrophy, in addition to the severe right ventricular hypertrophy. The R wave in Lead V_6 is 24 mm., again supporting evidence of left ventricular hypertrophy. The T waves in Lead V_6 are upright and do not suggest left ventricular strain. The P wave in Lead III is 3 mm., suggesting right atrial hypertrophy. While there is no broad notching of the P waves reflecting left atrial potentials, there is inversion of the P wave in Lead V_4R and V_1, and a diphasic P wave in Lead V_2. These changes suggest additional left atrial hypertrophy. The electrocardiogram, therefore, shows severe right ventricular hypertrophy with associated left ventricular hypertrophy. In addition, there is right atrial hypertrophy and probably left atrial hypertrophy. This electrocardiogram is not consistent with severe coarctation at six months of age, because generally by this time the right ventricular hypertrophy has decreased and, more significantly, left ventricular hypertrophy has appeared. The electrocardiogram does help in ruling out glycogen storage disease of the heart because of the normal PR interval and the absence of the equiphasic voltages in the precordial leads. A severe electrolyte disturbance is also ruled out and, while we cannot be absolutely certain that endocardial fibroelastosis is not present, the normal T wave axis and the upright T waves in Lead V_6 are evidence against this diagnosis. The protocol tells us that a thoracic roentgenogram showed left ventricular predominance with pulmonary vascular congestion at six months of age. May we see the films at this time?

Dr. S. H. Tsai:*

The chest film at the time of birth was within normal limits. The next film (Figure 3a) was taken at three months of age and shows definite car-

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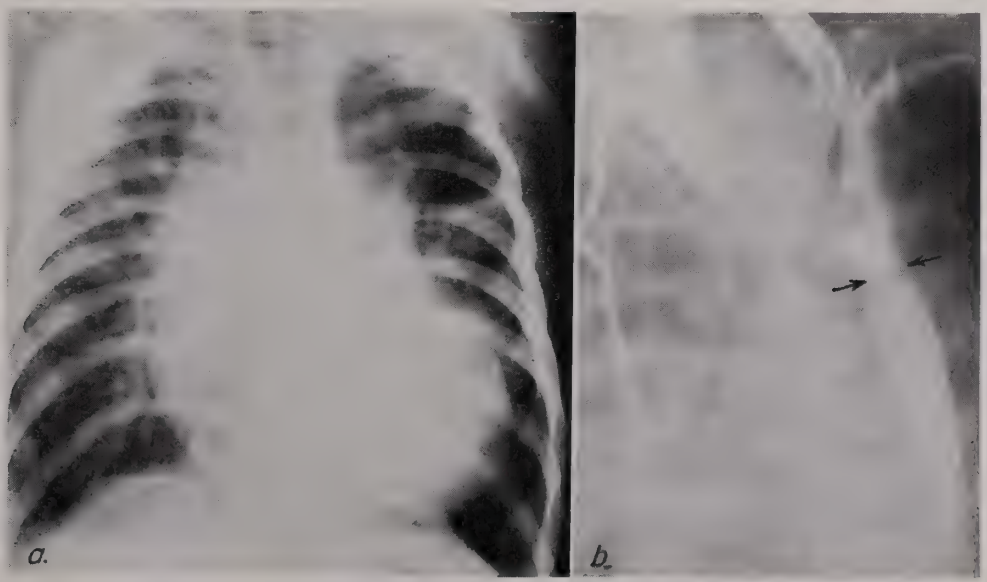


Fig. 3—(a) Frontal view of thoracic roentgenogram. (b) Aortogram, coarctation of aorta (between arrows).

diac enlargement and pulmonary vascular congestion which is more likely a result of venous congestion rather than increased blood flow. This film shows enlargement of the left atrium and also of the left ventricle. There is no positive evidence for right ventricular enlargement. Studies at six months of age continued to show cardiomegaly and pulmonary congestion.

Dr. Gathman:

A retrograde aortogram was then performed from the right brachial artery. This undoubtedly confirmed the presence of coarctation of the aorta which was clinically diagnosed on the second day of life. May we see the aortogram?

Dr. Tsai:

A retrograde aortogram was performed from the right brachial artery (Figure 3b). This confirmed the clinical impression of coarctation of the aorta which seemed clinically apparent on the second day of life. The ascending aorta did not become opacified in any of the films.

Dr. Gathman:

Because of increasing decompensation, the infant was sent to surgery, which was uneventful and presumably resulted in a good repair of the coarctation, with equal blood pressures in the arms and legs postoperatively. A systolic blood pressure of 130 mm. in the postoperative period is not very unusual, even in an infant, and would help me to rule out associated renal artery stenosis. Postoperatively he deteriorated with evidence of increasing congestive heart failure and the development of moist rales over both lung fields. Other than the chest film, this is the first definite evidence we have of left-sided congestive heart failure. The patient was not in electrolyte imbalance and, despite intensive medical management, he expired 24 hours postoperatively.

We now have the difficult task of synthesizing the information given to us in the protocol in order to explain why this child died postoperatively. One of the frequent defects occurring with coarctation of the aorta, patent ductus arteriosus, has been ruled out by the aortogram. Transposition of the great vessels has also been ruled out by the absence of cyanosis and the normal position of the aorta. Glycogen storage disease has been ruled out by the electrocardiogram. Endocardial fibroelastosis is also unlikely.

What then caused the severe pulmonary hypertension present in this patient? It could have been an associated ventricular septal defect; however, usually coarctation repair results in clinical improvement by decreasing left ventricular pressure. It would also be unusual for a patient with coarctation and a ventricular septal defect to have biventricular hypertrophy; pure right ventricular hypertrophy is more frequent. Pulmonary venous congestion is also not usually present. An associated atrial septal defect should again have been helped by coarctation repair. We must, therefore, direct our attention to associated defects of the left side of the heart, and in this patient the chest film beginning at three months of age showed predominantly left-sided congestive heart failure.

Cor triatriatum is a possibility; but left atrial hypertrophy on the electrocardiogram, even in the presence of coarctation, would tend to argue against this diagnosis. Abnormalities of the mitral valve may be present with coarctation; however, no diastolic murmur has been mentioned and, while

this need not be present with congenital mitral stenosis or parachute mitral valve, I would have expected this patient to have been in trouble sooner from a clinical standpoint. Congenital or acquired mitral insufficiency associated with endocardial fibroelastosis or infarction of the papillary muscles is unlikely because of the absence of significant ST-T wave changes. Therefore, it seems unlikely to me that this patient had hemodynamically significant mitral valvular disease.

Although we are not told so by the protocol, I feel that this patient was left with a systolic ejection murmur after the coarctation was repaired. Abnormalities of the aortic valve ranging from a bicuspid valve to aortic atresia have been reported in as many as 85 percent of cases with coarctation of the aorta and I would anticipate that this patient had a bicuspid aortic valve. I was hoping that the aortogram would rule out supravalvular aortic obstruction; however, it did not. There is no mention in the protocol of any abnormal facies or evidence of idiopathic hypercalcemia, and I think this helps in ruling out the hypercalcemia syndrome. It would also be extremely unusual for a patient with idiopathic hypercalcemia and supravalvular aortic stenosis to develop symptoms of severe congestive heart failure at this young age.

I have not yet explained his down-hill course after the repair of the coarctation, but I doubt that a significant degree of aortic valvular stenosis was present, on statistical grounds alone. In a recent publication Rowe and Mehrizi[1] describe a syndrome of coarctation of the aorta, subaortic stenosis, and other left-sided lesions as being differentiated by a murmur low along the left sternal border, a split-second sound with a markedly accentuated pulmonic component, and an enlarged heart with increased pulmonary vascularity. I would, therefore, like to conclude that the hemodynamically significant lesions in this child were: (1) coarctation of the aorta and (2) subvalvular aortic stenosis. I think the clues that would have helped me to make this diagnosis antemortem were the extremely loud pulmonic second sound and the evidence of severe pulmonary hypertension persisting at six months of age. I feel the loud systolic murmur heard best at the left sternal border is also significant.

In the terms of the clinical management of this patient, it would appear that he was handled very well. My only suggestion that might have helped to further evaluate his problem would be a left ventriculogram at the time of the aortogram.

Clinical Diagnoses:

1. Coarctation of the aorta.
2. Congenital subaortic stenosis.

Dr. Jesse E. Edwards:*

The essential findings at necropsy were found in the thorax, particularly in the heart and great vessels (Figures 4 and 5). There was evidence of resection of coarctation of the aorta with an end-to-end anastomosis, resulting in a lumen almost as wide as the aorta proximal and distal to the site of coarctation. Cardiomegaly was a feature in which the heart was somewhat more than twice normal weight. The major reason for the cardiac enlargement was hypertrophy of the myocardium of each ventricle.

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*Director of Laboratories, The Charles T. Miller Hospital, St. Paul; Clinical Professor of Pathology, School of Medicine and Professor of Pathology, Graduate School, University of Minnesota, Minneapolis; and Consultant, Hennepin County General Hospital, Minneapolis.

In the outflow tract of the left ventricle beneath a congenital bicuspid aortic valve the hypertrophied muscle protruded somewhat toward the left ventricular cavity, suggesting an element of hypertrophic muscular subaortic stenosis. In the left ventricle the arrangement of the papillary muscles was abnormal. This was characterized by the fact that, although two muscles were present, these were closely aligned and inserting into the lateral wall of the left ventricle. No papillary muscles were present at the junction of the posterior and septal walls. The mitral valve possessed two leaflets and the chordae inserted into the closely aligned papillary muscles. The appearance of the papillary muscles approached that seen in the parachute mitral valve, although the convergence of the chordae toward a single papillary muscle was not as striking as in classic examples of the parachute mitral valve, since two papillary muscles were present. Attached to the basal aspect of the atrial surfaces of the mitral leaflets was a low ridge of fibrous tissue which protruded into the lumen at the inlet to the mitral valve. Although this condition bears the name supravalvular ring of the left atrium and, although in some instances this lesion may cause severe obstruction to egress of blood from the left atrium, in this case it did not seem to be a significant feature in view of the minimal extent of this lesion. The left atrial chamber was dilated, the wall was hypertrophied, and the endocardium was distinctly thickened.

A ventricular septal defect was observed beneath the aortic valve, the defect centering beneath the right aortic cusp. Instead of leading into the right ventricle this defect led through a cleft in the tricuspid valve and to the right atrium, the aggregate representing a left ventricular-right atrial canal. Pouch-like structures were attached to the tricuspid valve, the de-

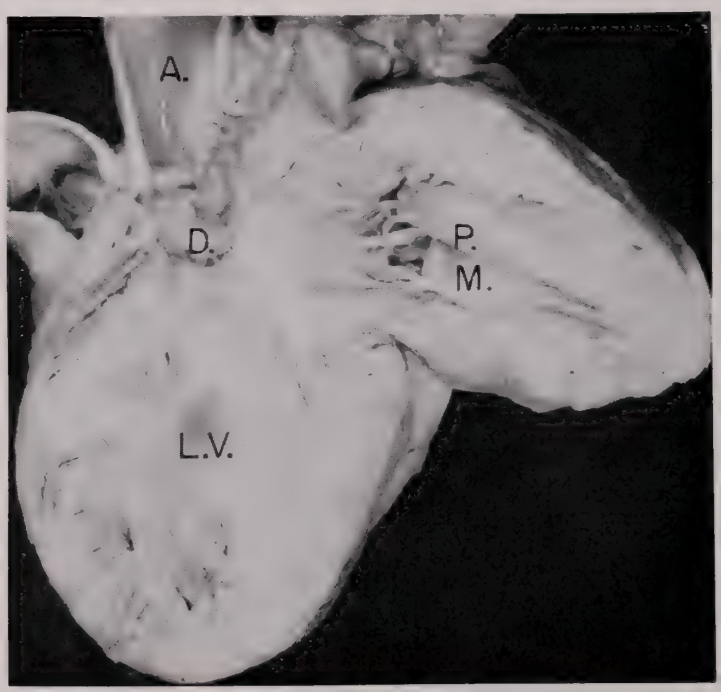


Fig. 4—Left ventrical (L.V.) and ascending aorta (A). Major hypertrophy of the left ventricular wall with prominence in the subaortic area. Defect (D.) is present in the ventricular septum and leads to a left ventricular-right atrial communication. The two papillary muscles (P.M.) lie closely aligned and insert into the lateral wall of the left ventricle.

tails of which were reported by Chesler and associates.[2] The right ventricular wall was hypertrophied and, in the outflow portion, the stout muscle bundles encroached upon the lumen, suggesting the presence of an element of right ventricular outflow obstruction. In essence, in this case there is a phenomenon of major muscular hypertrophy with a prominence in the subaortic area that may have caused subaortic stenosis and prominence in the subpulmonary area which may have been associated with some infundibular stenosis, although we do not have the catheterization data to prove these points. The muscular hypertrophy may represent idiopathic myocardial hypertrophy, for want of a better name.

As we discuss this case in relation to the pathologic findings as they relate to the clinical features, there was a coarctation of the aorta; but after the coarctation was corrected, there was still a problem of pulmonary venous obstruction. There was an element of a left-to-right shunt through the left ventricular-right atrial communication which, of itself, may not have been of major significance. What seems to have been important is the major hypertrophy of the left ventricle which probably caused a barrier to the free flow into the left ventricle; in this way, the muscular hypertrophy would constitute a situation very similar to that in mitral stenosis. There may also be an element of inflow obstruction into the right ventricle on the basis of the major hypertrophy of the right ventricle and in each ventricle, in addition, an element of outflow obstruction. In this case, the presence of coarctation of the aorta, supravalvular ring of minor degree, a deformity of the mitral valve in the direction of a parachute mitral valve, and the presence of subaortic stenosis call to mind a syndrome recognized here in the Twin Cities several years ago. Finally reported by Shone and others, we call it the Shone syndrome.[3] It has four obstructive anomalies in the left side of the heart: supravalvular ring of the left atrium,

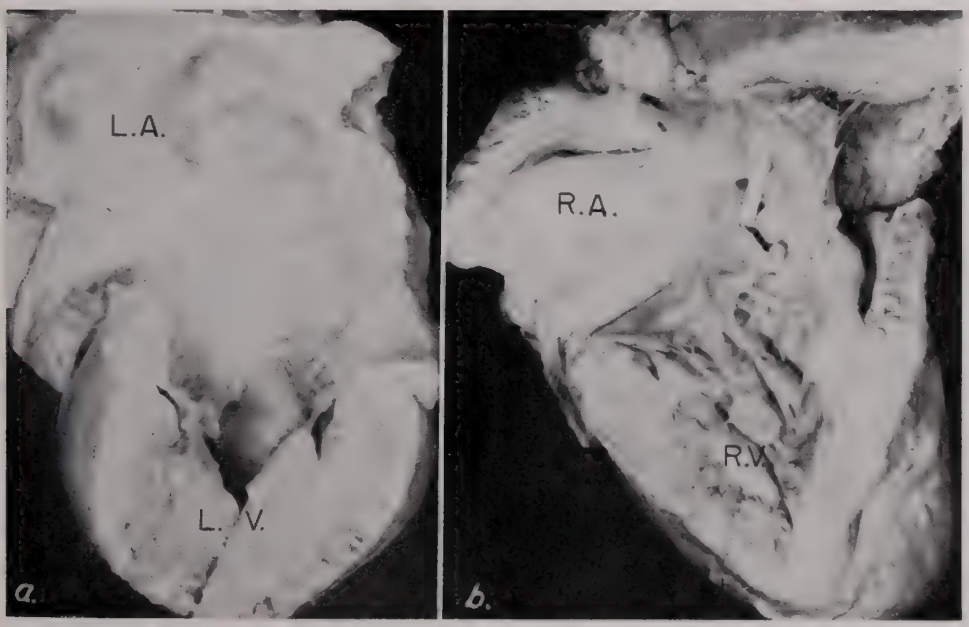


Fig. 5—(a) Left atrium (L.A.) and left ventricle (L.V.). The left ventricular myocardium shows major hypertrophy. The left atrial chamber is enlarged, its endocardium thickened and its myocardium hypertrophied. (b) Right atrium (R.A.) and right ventricle (R.V.). A cleft in the tricuspid valve allows a left ventricular-right atrial communication (probe). Major hypertrophy of the right ventricular wall associated with suggestion of infundibular stenosis.

parachute mitral valve, subaortic stenosis, and coarctation of the aorta.

I think this case illustrates the Shone syndrome. In the normal mitral valve, the two papillary muscles are quite a distance from each other and the chordae of the mitral valve diverge to insert into the two papillary muscles. In the classical parachute mitral valve there is one group of papillary muscles and, while there are two mitral leaflets, the chordae converge to insert into the single papillary muscle. Such a valve may be stenotic if the spaces between the chordae are small, as occurs in some cases. In the current case, I do not believe that the mitral anomaly contributed to mitral stenosis. A supravalvular ring was also present but was of minor proportion.

Among the eight cases that Shone reported, there was variation in how severe each lesion was and also in how many of the four elements of the syndrome were present in any one case. In one case, there was the complete picture from the point of view of the anatomic lesions and the functional significance of each. In some other cases all four lesions were present, but in none was each lesion functionally significant. In the case presented, I would say the supravalvular ring and the mitral deformity were not significant, the subaortic stenosis was of questionable significance, and the coarctation was obstructive. The diffuse myocardial hypertrophy was probably the significant factor in causing pulmonary venous obstruction. It is of interest that the left ventricular-right atrial communication present in the case today is not the first seen in conjunction with the Shone syndrome. In Shone's series there was a 13-year-old child with a left ventricular-right atrial communication which was closed at operation. In the case presented, the shunt through the left ventricular-right atrial communication would serve to compound the effects of the hypertrophied left ventricle in causing pulmonary venous obstruction.

Also, a fairly heavy thread of bicuspid aortic valve runs through the cases. It is interesting that in one of Shone's cases without coarctation, a bicuspid aortic valve was present. We may close this discussion by making the generalization that coarctation of the aorta may be a serious condition in infancy and its presence may mask the presence of additional conditions. Another axiom is that if a coarctation is properly repaired and the patient continues to have symptoms, there is some additional condition present. Some of you who read the old literature might say that is just as we expected because the old idea was that, in the presence of a symptomatic infant with coarctation, there most certainly would be another condition. We know that this is not true, because there are patients who have coarctation as the only significant abnormality. Yet others have other conditions. Therefore, one does have to exercise an awareness of the possibility of other conditions present in the symptomatic infant with coarctation. It is convenient to know about the Shone syndrome, since among some of the patients with coarctation who have continued trouble after the coarctation is resected, one or another element of the four lesions of the Shone syndrome may contribute to the trouble.

Diagnoses:

1. Coarctation of aorta.
2. Idiopathic cardiac hypertrophy with muscular subaortic and subpulmonary stenosis.
3. Supravalvular ring of left atrium.
4. Parachute mitral valve.

5. Left ventricular-right atrial communication.
6. Bicuspid aortic valve.
7. Pouches of tricuspid valve.

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His Nganga* Failed

Francis:† a MuZezuru from Enkeldoorn, aged thirty. He suffered from epilepsy and had his first fit in 1950 and since then had had an attack every three years. A year before coming to hospital, he had consulted a diviner who told him that the spirit of his late wife was annoyed with him for refusing to marry her sister; it was so annoyed that it was operating as an angered spirit—a ngozi. First it troubled her own parents and they consulted a nganga who diverted it back to Francis; it was then that his epilepsy started. In 1959 he married his sister-in-law but he still suffered from fits, so he sought advice from a nganga who suggested that he chase the ngozi back to his father-in-law, and gave him herbal remedies for the fits. Francis took the medicine, but up to the time he came into the hospital he had not arranged with the nganga to drive the ngozi to his father-in-law.‡

*Nganga—Southern Rhodesian witch doctor.

†Francis was admitted to a Southern Rhodesian hospital after his nganga failed to cure him.

‡Michael Gelfang: Witch Doctor, 1965.

Disease as Reprisal III

Why was Gehazi smitten with leprosy?

Under false pretenses he had requested and received from Naaman a gift of money and clothing, a sin he subsequently failed to confess to his master, Elisha, who then proclaimed:

The leprosy therefore of Naaman shall cleave unto thee, and unto thy seed for ever. And he went out from his presence a leper white as snow. (II Kings 5:27)

To forgive and forget means to throw valuable experience out the window.
—Schopenhauer

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Advance

Neurotoxicity of Antibiotics

THE USE OF antibiotics is occasionally compromised by various neurotoxic reactions that involve the peripheral nervous system as well as the central nervous system.

The mechanisms of antibiotic action are incompletely understood. The substances, produced by living organisms, inhibit the growth and activity of other living organisms.[1] To be clinically useful, antibiotics must cause little or no harm to the host. Some, such as penicillin, inhibit the synthesis of the bacterial cell wall; whereas others, such as the polymyxins, disrupt the bacterial cell membrane, a structure functionally distinct from the cell wall. Antibiotics also act by affecting bacterial protein synthesis (chloramphenicol, tetracyclines), nucleic acid metabolism, and intermediary metabolism of the bacteria.[1-4] The mechanisms that cause antibiotic neurotoxicity may differ considerably from the mechanisms of antibiotic action on microorganisms.

Adverse drug reactions may be: (1) toxic reactions related to excessive dosage, (2) side reactions due to an unintended pharmacologic effect of the medication, (3) allergic reactions, and (4) idiosyncrasies to the drug that are unrelated to dosage or allergy.[5,6] The mechanisms underlying the various neurotoxic effects are not fully understood, but the reactions are of different types. Among the neurotoxic effects are cochlear damage, vestibular damage, block of neuromuscular transmission, optic neuritis, seizures, arachnoiditis, peripheral neuropathy, and miscellaneous reactions.[7] Other reactions associated with non-antibiotic antimicrobial drugs such as the sulfonamides and isoniazid will not be discussed.

Cochlear Damage

Hearing loss is caused most often by derivatives of *Streptomyces* organisms, including dihydrostreptomycin, kanamycin, neomycin, vancomycin, viomycin, and to a lesser extent, streptomycin. Other antibiotics that cause auditory impairment include gentamicin, colistin, and framycetin.[8-10]

The hearing loss that results from antibiotic toxicity is due to degeneration in the organ of Corti and its sensory receptors. Hawkins and Lurie[11] explained the selective toxicity to the eighth cranial nerve of dihydrostreptomycin and neomycin on the basis of the special access of these antibiotics to the inner ear by way of cerebrospinal fluid and perilymphatic channels. This was demonstrated by the greatly increased severity and decreased latency of the ototoxic effect of moderate doses of parenterally administered streptomycin and dihydrostreptomycin, when supplemented by the intracisternal injection of minute amounts of the appropriate drug.

Engström and Kohonen,[8] studying the human cochlea, demonstrated that kanamycin, neomycin, and framycetin first damaged the outer hair cells at the basal end of the cochlea, the sensory endings for high-frequency hearing. The degree of destruction of the hair cells in the basal coil was directly related to dosage and length of treatment. Inner hair cells were damaged much later than outer ones and were first destroyed at the top coil of the cochlea. Damage to supporting elements also occurred with increasing dosage. Hawkins,[12] studying kanamycin in animals, was unsure whether the initial changes were in the hair cells or in the supporting cells of the organ of Corti. Degeneration of nerve tracts in the central nervous system has not been encountered without loss of sensory epithelium, thus indicating the peripheral origin of the toxic damage.[13]

*This paper was prepared under the supervision of members of the faculty of the Mayo Graduate School of Medicine.

Stupp and associates[14] have shown that the level of kanamycin in labyrinthine fluid increases more rapidly than the level in serum and is not directly related to the dosage. The maximal concentration in the inner ear is reached at the relatively small dose of 50 mg/kg, and the concentration is not increased by a dose five times greater. However, a significant increase in concentration of kanamycin in labyrinthine fluid is demonstrated if the higher dose is given for 10 to 20 days.

A major factor in the antibiotic concentration in plasma is the rate of excretion. Delayed excretion results in higher serum levels and increases the chance of adverse drug reactions.[10] Patients with pre-existing renal damage are more likely to experience toxic effects of drugs excreted by the kidney. Because all of the drugs previously mentioned, except framycetin, are nephrotoxic, renal impairment may develop during therapy.

Recent histochemical studies indicate that the ototoxic antibiotics probably impair glucose metabolism and interfere with the energy supply of the sensory cells in the inner ear.[10]

Clinically, cochlear damage due to antibiotic toxicity begins with loss of high-frequency hearing, the loss being demonstrable by audiometry.[7] Tinnitus or a feeling of fullness in the ear may precede this loss in about half the cases.[9] The hearing loss worsens to include the lower frequencies and can result in total deafness.[10] Once these changes occur, they are usually permanent, although a few patients have had return of partial hearing after cessation of kanamycin therapy.[15] The damage may occur after a latent period and may increase after the use of the antibiotic has been discontinued, especially when drug excretion is impaired. This is especially true with dihydrostreptomycin, but not with kanamycin.[9,15]

Although individual sensitivity may be a factor, dosage and duration of administration seem to be most important in the production of cochlear damage by antibiotics. Maximal dosage limits are recommended for most of these antibiotics in order to minimize the possibility of hearing loss. The likelihood of antibiotic ototoxicity is greatest in infants, the aged, dehydrated patients, and those with impaired renal function.[7] Hearing loss has occurred in infants of mothers treated with streptomycin during pregnancy.[16]

Ototoxicity may be associated with administration of these drugs by any route. It is generally recommended that combinations of ototoxic drugs not be given concurrently or in succession. In long-term therapy, such as for tuberculosis, intermittent administration is suggested.[7]

Vestibular Damage

Antibiotic-induced vestibular damage is closely related to cochlear toxicity. Streptomycin is the most common antibiotic that produces vestibular dysfunction, but most of the antibiotics that cause hearing loss may also lead to vestibular changes. Why streptomycin acts differently in predominantly affecting the vestibular sensory organs in the inner ear is unexplained. Streptomycin may also damage cochlear structures, resulting in hearing loss.[17]

Vestibular toxicity from streptomycin is directly related to dosage and duration of administration,[18] though individual sensitivity, rate of excretion, age, and state of hydration are also factors. The mechanism is unknown, although inhibition of glucose metabolism supplying energy for the end-organ cells by the drug has been suggested.[10] The vestibular damage is usually bilaterally symmetric, although asymmetric or even unilateral damage has been reported.[9]

Clinically, vestibular toxicity from streptomycin causes disturbance of gait and vertigo associated with head movements. Although the pathologic changes are apparently irreversible, symptoms often seem to gradually diminish, perhaps partly because of compensation by visual mechanisms.[7]

Block of Neuromuscular Transmission

An interesting peripheral neurotoxic effect of some antibiotics is blockade of neuromuscular transmission. Antibiotics that may do this are neomycin, streptomycin, dihydrostreptomycin, polymyxin A and B, kanamycin, colistin, viomycin, and paromomycin.[19,20]

The mechanism of neuromuscular transmission blockade is unclear. Elmqvist and Josefsson,[21] studying neomycin-produced neuromuscular block in laboratory preparations by extracellular and intracellular recording techniques, observed that the block was due to a

reduction in amplitude of the end-plate potential. This was caused, in part, by a decrease in sensitivity of the post-junctional end-plate membrane to the depolarizing action of acetylcholine. They also found that neomycin reduced the amount of acetylcholine released after stimulation of the motor nerve. This effect was antagonized by an excess of calcium ions. They believed the most likely explanation of the pre-junctional action of neomycin is that it, like magnesium, competes or interacts with calcium ions at some step in the release of acetylcholine. Brazil and Corrado,[22] studying neuromuscular transmission in dogs, noted many similar effects of magnesium ions and streptomycin.

Kubikowski and Szreniawski[23] reported that the depression of motor-nerve endings caused by several antibiotics is biphasic; there is a short initial phase of competitive blockade followed by a prolonged depolarization combined with calcium depletion. They stated that the same antibiotic probably could produce neuromuscular blockade by different mechanisms, depending on its duration and concentration in the vicinity of the end-plate.

Early clinical reports of antibiotic-induced neuromuscular blockade described respiratory depression after intraperitoneal and intrapleural administration of neomycin and streptomycin during surgery.[19] Gold and Richardson[24] reported the case of a 48-year-old woman who experienced ptosis, diplopia, and bilateral weakness in her shoulder girdle and arms within five hours after the intramuscular administration of colistin methanesulfonate (Coly-Mycin). Edrophonium chloride (Tensilon) reversed the weakness but had a variable effect on the ptosis. The symptoms occurred with a blood level of the antibiotic in the low therapeutic range and began to subside within eight hours after drug injection. The patient showed no evidence of myasthenia gravis on electrophysiologic studies during an antibiotic-free period.

The neuromuscular blocking action of the antibiotics previously mentioned may be potentiated by drugs such as ether or other anesthetic agents, muscle relaxants, sedatives, or narcotics.[24,25] The antibiotics may aggravate the weakness in patients with myasthenia gravis.[26]

Treatment of antibiotic-induced neuromuscular blockade includes support of respiration, cessation of therapy with the implicated antibiotic and possible potentiating drugs, and use of neostigmine or calcium or both.[25]

Optic Neuritis

Optic neuritis occurs occasionally in association with chloramphenicol or streptomycin therapy, apparently due to a deficiency of vitamin B, possibly of pyridoxine.[7,27-29] Some authors have questioned the cause-and-effect relationship of antibiotics and optic neuritis, stating that the toxic phenomenon may be related to the basic disease process or to an associated nutritional deficiency.[30]

The optic neuritis causes loss of visual acuity, constriction of visual fields, scotomata, papilledema, and retinal hemorrhages. Usually, though not always, vision improves when the use of the drug is discontinued and therapy with vitamin B is given concomitantly. Cocke[27] has reported possible benefit with prophylactically administered pyridoxine and vitamin B_{12}, given with chloramphenicol, in a patient who had cystic fibrosis and who had had two previous episodes of chloramphenicol-induced optic neuritis.

Seizures

The irritating effects of penicillin on the central nervous system, first described by Johnson and Walker[31] after intraventricular administration in a case of meningitis, may consist of muscular hyperirritability, myoclonic jerking, generalized seizures, coma, and death.[32,33]

Penicillin rarely crosses the blood-brain barrier in the normal person, but when meningeal inflammation is present, higher concentrations of the drug in the cerebrospinal fluid occur with systemic administration.[34] Neurotoxicity rarely occurs unless the dose exceeds 60 million units per day,[35] or unless renal insufficiency is also present.[36] Direct administration of penicillin into the cerebrospinal fluid is more likely to cause neurotoxicity; this is particularly true of intraventricular or intracisternal injections.[32,37] Weinstein[33] recommends that dosages above 30,000 units should not be injected into the subarachnoid space in adults, and that lesser dosages should be used

in children.

Cycloserine, in doses greater than 1 gm/day, has been reported as causing myoclonic jerking and epileptiform seizures. These effects are rapidly reversible after the use of the drug is discontinued.[30,38]

Arachnoiditis

Arachnoiditis with radiculopathy and myelopathy may occur as a complication of the intrathecal injection of any chemical agent, including antibiotics.[37,39,40] Recommendations to prevent or minimize this neurotoxic reaction of amphotericin B, administered intrathecally for fungal meningitides, include use of small, well-controlled amounts of the drug, intrathecal administration of corticosteroids prior to the use of the antibiotic, and alteration of intrathecal injection sites—lumbar and cisternal areas.[40]

Fortunately the intrathecal use of antibiotic agents is rarely necessary in the treatment of bacterial meningitis now, unless the physician is confronted with a *Pseudomonas* meningitis that requires the use of polymyxin, or a severe pneumococcal meningitis that requires the use of penicillin. In tuberculous meningitis, intrathecally administered streptomycin is no longer used, but in previous years this drug has caused arachnoiditis in some patients.

Peripheral Neuropathy

Peripheral neuropathy has occurred during treatment with streptomycin, dihydrostreptomycin, neomycin, kanamycin, chloramphenicol, polymyxin B, colistin, and amphotericin B. Some of these toxic neuropathies may be related to depletion of pyridoxine. They are sensorimotor in character and reversible if the antibiotic therapy is discontinued soon after the onset of symptoms.[7,29]

Circumoral and distal paresthesias may develop during therapy with streptomycin, dihydrostreptomycin, neomycin, kanamycin, polymyxin B, and colistin. Usually these symptoms are ameliorated even when therapy is continued, and they generally disappear when the therapy is stopped.[7,41]

Mononeuropathy occurs from inadvertent injection of an antibiotic into a peripheral nerve, producing chemical injury that may persist indefinitely.[18]

Miscellaneous Reactions

Nonspecific reactions such as headache, insomnia, weakness, and drowsiness may occur while a patient is receiving antibiotics. Penicillin and cycloserine may be associated with personality changes and acute psychoses.[7,38]

Tetracycline therapy in infants has been associated with increased intracranial pressure; the pressure disappears when the use of the drug is discontinued. No relationship was noted between the occurrence of bulging fontanelle and either the dose or the length of therapy.[42]

Conclusion

Antibiotic neurotoxicity results from factors that influence the metabolism, neutralization, and excretion of antibiotics; these factors include the specific drug, route of administration, dose and duration of therapy, and the physiologic deficit of the patient.[43]

The most common neurotoxic effect is damage to the auditory and vestibular apparatus, generally by antibiotics derived from *Streptomyces* organisms. Usually these reactions are related to dose and duration of treatment. Disturbed physiologic functions of the patient, such as impairment of renal function, are important factors in determining the dose that a patient may tolerate.

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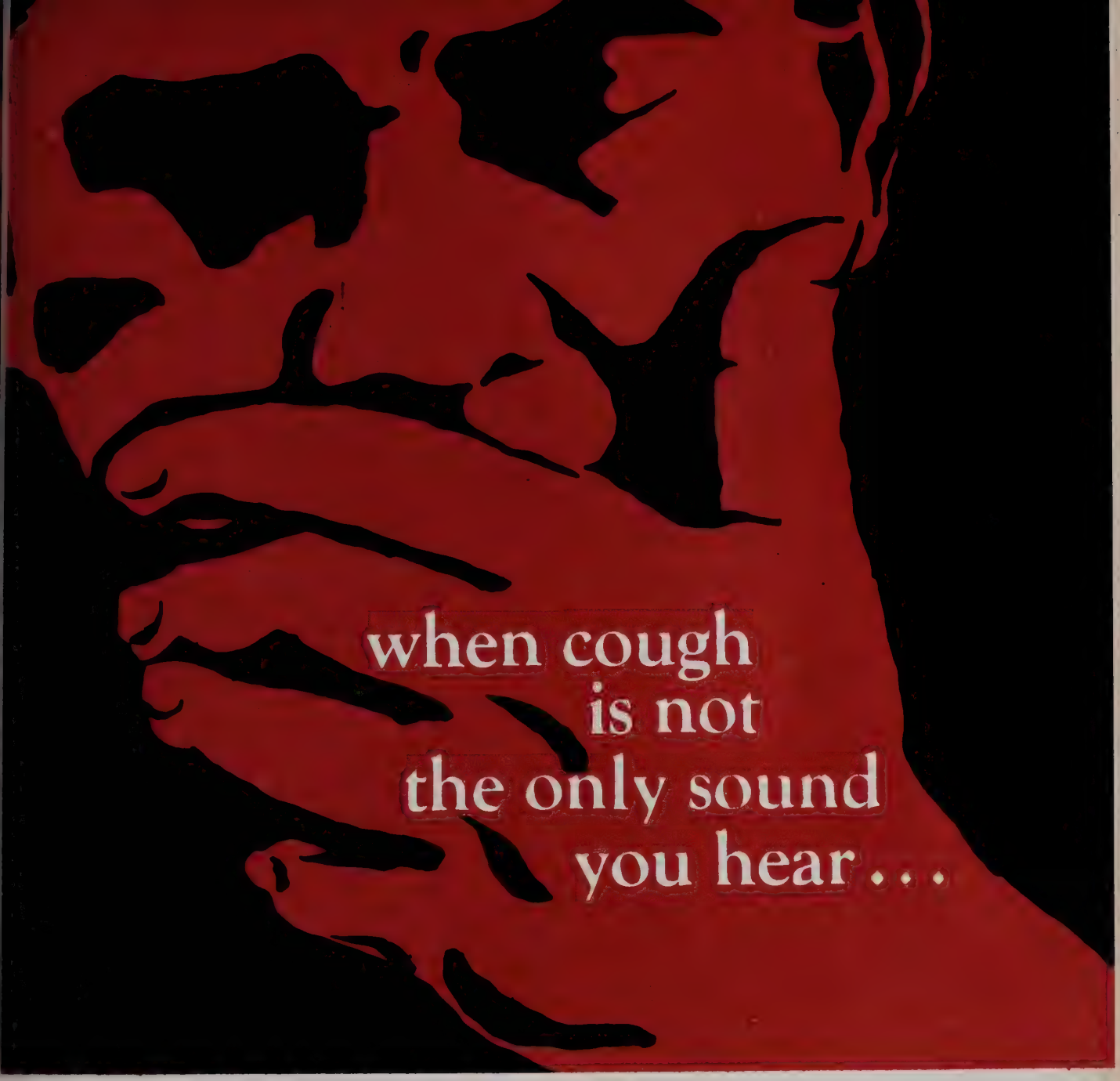
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No brain is stronger than its weakest think.—Tom Masson



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Contraindications: Hypersensitivity to any component.

Warning: In renal impairment, since liver toxicity is possible, lower doses are indicated; during prolonged therapy consider serum level determinations. Photodynamic reaction to sunlight may occur in hypersensitive persons. Photosensitive individuals should avoid exposure; discontinue treatment if skin discomfort occurs.

Precautions: Drowsiness, anorexia, slight gastric distress can occur. In excessive drowsiness, consider longer dosage intervals. Persons on full dosage should not operate vehicles. Nonsusceptible organisms may overgrow; treat superinfection appropriately. Treat beta-hemolytic streptococcal infections at least 10 days to help prevent rheumatic fever or acute glomerulonephritis. Tetracycline may form a stable calcium complex in bone-forming tissue and may cause dental staining during tooth development (last half of pregnancy, neonatal period, infancy, early childhood).

Adverse Reactions: *Gastrointestinal*—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. *Skin*—maculopapular and erythematous rashes; exfoliative dermatitis; photosensitivity; onycholysis, nail discoloration. *Kidney*—dose-related rise in BUN. *Hypersensitivity* reactions—urticaria, angioneurotic edema, anaphylaxis. *Intracranial*—bulging fontanels in young infants. *Teeth*—yellow-brown staining; enamel hypoplasia. *Blood*—anemia, thrombocytopenic purpura, neutropenia, eosinophilia. *Liver*—cholestasis at high dosage.

Upon adverse reaction, stop medication and treat appropriately.

Lederle

927-8



Grand Rounds

Pernicious Anemia vs. Gastric Carcinoma*

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PERNICIOUS ANEMIA is a chronic disease, generally affecting people past middle age. It usually produces hematologic, gastrointestinal, and neurological manifestations. Before the discovery of liver therapy, its course, even though interrupted by exacerbations and remissions, was uniformly fatal; thus the name "pernicious anemia" was coined. Now with specific therapy this disease is virtually never fatal, but the name, pernicious, remains.

The clinical features of pernicious anemia were first described by Addison in 1855. Fenwick, in 1880, suggested that inadequate digestion and utilization of food was the basic problem.[1,2] Minot and Murphy, in 1926, demonstrated the value of liver therapy in patients with pernicious anemia,[3] and Castle's experiments in 1929 brought into focus the etiologic concepts in regard to intrinsic and extrinsic factor in the pathogenesis of this disease.[4]

Incidence

Although this disease is seen chiefly in Caucasians and is more common in persons of Scandinavian ancestry, it occurs in all peoples. Its incidence in Negroes is low but not as low as previously thought.[5] It is a disease of adult life and, in this country, more common in women than men.

Pathogenesis

The mucosal (parietal cell) glands of the fundus of the stomach secrete a glycoprotein known as intrinsic factor, which is necessary for the absorption of vitamin B_{12}.[22] The normal amount of absorption in the adult is 1 to 2 mcg/day. Loss of intrinsic factor secretion leads to the inability of the ileum to absorb vitamin B_{12}, and in turn to a B_{12} deficiency state. When the capacity

*Presented as a Medical Grand Rounds at Hennepin County General Hospital, May 7, 1968.
†Currently on active duty, United States Naval Hospital, Oakland, California.

to absorb vitamin B_{12} is abruptly lost in an otherwise healthy individual (e.g., after total gastrectomy), the clinical manifestations associated with B_{12} deficiency usually develop in about three years.

Vitamin B_{12} is found in many tissues of the body, the highest concentration being in the liver. It is interesting that there is no good evidence that B_{12} shifts from the liver to other organs when a deficiency is present; in fact, in complete relapse of pernicious anemia, the B_{12} content of the liver when measured is only 10% of normal.[22] This suggests that in pernicious anemia there is some block of release of B_{12} from the liver.

Clinical Manifestations

The classical diagnostic triad in pernicious anemia is weakness, sore tongue, and parasthesias; usually numbness and tingling of the extremities. However, with diagnostic tests to help us detect the disease earlier, the classic findings may be absent.[6] Weakness seems to be the most common presenting symptom, and glossitis is present in about 10% of cases. With severe anemia, the skin's color turns to a light lemon yellow. Very often there will be premature greying or blond hair. Even though there is a thrombocytopenia, petechiae are unusual. Vitiligo may also be present.

Fever elevation up to 102° is not uncommon and generally remits when treatment is started. Semi-solid bowel movements, two to three per day, are a common finding. The liver is usually slightly enlarged, and splenomegaly is reported in various series from 3% to 40%.[7]

Neurologic involvement from pernicious anemia is commonly seen.[1,5] Complaints usually consist of generalized weakness, numbness, and tingling of the extremities that may lead to difficulty in navigating. Peripheral nerve degeneration as well as spinal cord degeneration may occur.[8] Numbness and a "glove-stocking" type of paresthesia may develop as a result of peripheral nerve damage. The spinal cord degeneration usually starts in the posterior columns, but then goes on to involve the lateral columns as well. When the distal and lateral columns are both involved, ataxia and some spasticity may be present. Altered mentation* is usually noticeable, with irritability, apathy, memory loss, and somnolence being the most common symptoms. Loss of vibratory sense and position sense is frequently noted.

Laboratory Findings[1,5]

Peripheral Blood

The peripheral blood findings generally include all the formed elements: red cells, white cells, and platelets. The red cells usually show macrocytic changes. The cells may be oval in shape and, due to basophilia, stain a blue-grey color. Poikilocytosis is usually present. Generally the more pronounced the anemia the more bizarre the shapes that are seen. The cells, whether small or large, normal or bizarre, are usually well filled with hemoglobin and generally do not have a central pale zone. Occasional Howell-Jolly bodies may be found. Reticulocytes are usually not seen, except in response to therapy. It is an error to assume that the red blood cells in pernicious anemia are supersaturated with hemoglobin; the concentration of hemoglobin in these cells is the same as in normal red cells, about 32% to 36%.

The leukocytes may be larger than normal and multi-segmented. These lobes may have bizarre shapes and the chromatin bridges connecting them

*See Test Your Word Score Page 1583.

may be thin and stringy. The nuclear matter may appear looser than normal, and the cytoplasmic granulation may be more acidophilic and larger than normal. These changes in the white cells may be the first peripheral blood changes to occur in pernicious anemia. There is usually an absolute neutropenia as well as a relative lymphocytosis. Immature cells of the myeloid series may be present, but are usually only about 1% of all the leukocytes seen. Eosinophilia is seen occasionally.

The platelets are generally decreased in number and, as with the leukocytes, bizarre shapes may be noted.

Bone Marrow

The volume of the marrow in pernicious anemia is usually increased by the replacement of fat along marrow cavities and by the increased number of cells. Instead of the normal erythrocyte to myelocyte ratio of 1:4, the red cell hyperplasia may shift this to 1:1. Instead of the usual normoblastic proliferation of the red cell series, one sees a megaloblastic proliferation. The megaloblasts may be distinguished by their large size and their delicate nuclear chromatin; they may have very basophilic cytoplasm and not appear at all like members of the erythroblastic series, which generally lack cytoplasmic granulation and have large central neuclei and irregular borders. There are generally more megaloblasts than normoblasts. Abnormal leukopoiesis is also seen in the bone marrow of patients with pernicious anemia. There is usually an increase in myeloid leukocytes, and many large leukocytes may be noted. Megakaryocytes, besides being reduced in number, may also be abnormal in configuration.

Other Laboratory Abnormalities

There is also an inability to concentrate urine; the specific gravity is usually low and fixed. During relapse the serum alkaline phosphatase is low, while the serum lactic acid dehydrogenase activity is markedly increased.[8] The serum cholesterol is lower in relapse than in remission. There is usually a negative nitrogen balance in relapse, with decreased colloidal osmotic pressure of plasma, and mild water retention. Hypogammaglobulinemia may also be present.[1] There is generally a slight increase in serum bilirubin.

Gastric Findings

Gastrointestinal symptoms do not seem to be a common complaint in patients with pernicious anemia, although abnormalities of the gastrointestinal tract are usually seen. Histamine-fast achlorhydria is almost always found, except perhaps in infants and adolescents. The gastric mucosa is generally atrophic, and there is an increased incidence of gastric polyps. Small bowel biopsies in patients with pernicious anemia in relapse show a decrease in mitoses and a shortening of villi, as well as megaloblastic changes in the epithelial cells.[10] Administration of vitamin B_{12} will revert these changes to normal in about two months.

Basis for Auto-immunity

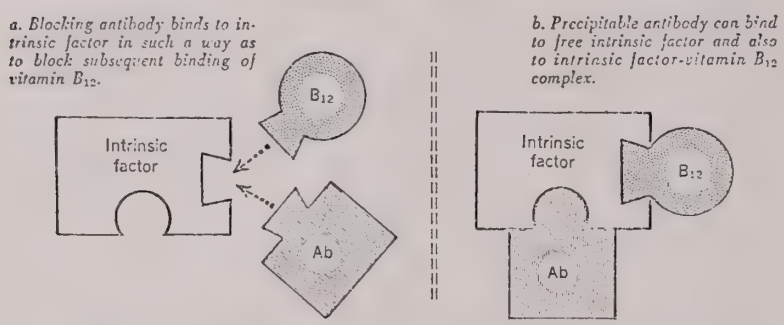
In attempting to determine an etiologic basis for pernicious anemia, much work has been done on the immunologic aspects of this disease. It is well established that acquired pernicious anemia is due to an inadequate amount or absence of intrinsic factor.[4,5] On gastric biopsy there is usually a reduction in the parietal cells, which in man are responsible for the secreting of intrinsic factor. In an attempt to differentiate these findings from a "pure"

atrophic gastritis, various screening tests were done to see if the two could be differentiated. It was found that patients with pernicious anemia have a high incidence of antibodies specifically against the parietal cell.[12,13,14] Ninety percent of patients tested had antibodies to the parietal cells, whereas patients with a pure type of atrophic gastritis showed an absence of antibodies either to the parietal cells or to intrinsic factor.[12] Herburt has reported that 60% of patients with pernicious anemia have antibodies against intrinsic factor, 90% against the parietal cell, and about 50% against the thyroid gland.[13,15,18]

The high incidence of antibodies detected in patients with pernicious anemia, in combination with histologic features of chronic inflammation and atrophic gastric mucosa, suggest that the disease may be an auto-immune disorder. This is in part substantiated by the high incidence of thyroiditis and myxedema in pernicious anemia.[16,20,21,23] No one, however, has established that these antibodies are harmful to gastric mucosa.[13] Antibodies to intrinsic factor have also been found in the saliva of patients with pernicious anemia.[17]

There are two types of antibodies to intrinsic factor that have been found in patients with pernicious anemia.[12,17,19] One seems to be directly related to intrinsic factor, while the other is directed against the parietal cell. The blocking antibody combines with intrinsic factor in such a way as to preclude the combination with B_{12} (Figure 1). The precipitable antibody can combine with intrinsic factor alone or in combination with B_{12}, and can then be precipitated by various gamma globulin precipitants.

Two functional classes of antibody to intrinsic factor.



*Herbert, V.: Immunologic Factors in Pernicious Anemia. Postgrad Med 42:300, 1967.

Figure 1

Evaluation of Pernicious Anemia at Hennepin County General Hospital from 1961-1967

During the seven-year period from 1961 through 1967 a total of 81 patients were admitted to Hennepin County General Hospital with proven pernicious anemia. Of these 81 patients, 48 were being seen for the first time, and the diagnosis of pernicious anemia was new; the other 33 had been followed here for an average of 10.7 years. Our series included 18 males and 33 females. The age range at the time pernicious anemia was diagnosed was 33 to 87, the mean age being 74. The diagnosis was established by peripheral blood morphology, abnormal Schilling test, or abnormal and characteristic bone marrow. At least two of the above criteria had to be positive for the

diagnosis to be accepted. All of the cases responded to administration of vitamin B_{12} except one patient, who also exhibited a relapse of monocytic leukemia.

Hemoglobin determinations at the time of diagnosis ranged from 2.9 to 10.9 grams. Bone marrow examinations were done in 33 patients, and all the interpretations were consistent with the changes seen in pernicious anemia. Decreased-to-absent iron stores were noted in over 75%.

Weakness of insidious onset was noted in almost all of our patients as an initial complaint. Leukopenia and thrombocytopenia were present in over three fourths. None exhibited any bleeding abnormalities. The maximal reticulocyte response to vitamin B_{12} occurred between the fourth and fifth day, the highest response being 39.8%, the lowest 2%. The patient with a 2% response had acute leukemia in relapse at the same time his pernicious anemia was noted to be in relapse. The peripheral smear was considered to be diagnostic in 37 of the 48 new patients in whom it was done. The Schilling test was made in 28 patients and was below 3% excretion in 26.

Six of our patients had co-existing carcinomas (Table 1). Two had hematologic malignancies; two, prostatic malignancies; one, colon carcinoma, and one, multiple myeloma. Two had gastric polyps, detected on gastroscopy; one was not noted on barium x-rays and three were hypothyroid. None had a diagnosis of carcinoma of the stomach.

TABLE 1

Patients at Hennepin County General Hospital with Pernicious Anemia and Associated Malignancies from 1961-1967

Malignancy	Number of Patients
Carcinoma of Prostate	2
Chronic Leukemia	2
Carcinoma, Colon	1
Multiple Myeloma	1
Other Non-Malignant Diseases	
Gastric Polyps	2
Hypothyroidism	3
Diabetes	2

Relationship of Pernicious Anemia to Gastric Carcinoma

That persons afflicted with pernicious anemia have a greater chance of developing cancer of the stomach than the general population has been suggested by several studies.[24,25,26] This increased incidence of gastric carcinoma is reported to be 1% to 18% higher than in the general population. Hitchcock, in following 1,399 patients for nine years who were achlorhydric but did not have pernicious anemia, concluded the incidence of gastric carcinoma to be 0.9% higher than in the normal population. He also followed 77 patients with pernicious anemia, of whom 5.2% later developed carcinoma of the stomach.[25] Patients over 50 years of age with pernicious anemia were expected to have an 18.3% increased incidence of gastric carcinoma, over the national average. It was therefore concluded and generally accepted that patients with pernicious anemia had a statistically greater chance of developing cancer of the stomach and should be closely followed.

The above studies were done from 1925 to 1950, when the general incidence of gastric cancer was much higher than now. While the incidence is

TABLE 2
New Pernicious Anemia Diagnosed at Hennepin County General Hospital: 1961-1967

	Age	Sex	Hgb.	Hct.	WBC	Max. Retic. Response	Morphology	Marrow	Schilling	Cancer of Stomach	Comments
1.	70	M	5.9	17.5	9600	20	Macrocytic	Megaloblastic	1.3%	0	
2.	75	M	7.5	23			Macrocytic	Megaloblastic	None	0	
3.	77	F	10.2	30			Macrocytic	Megaloblastic		0	
4.	61	F	9.8				Macrocytic	No		0	
5.	74	F	10.9				Macrocytic	No	1.4	0	
6.		F	4.5	14	2000	23.6	Macrocytic	Megaloblastic	1.3	0	
7.	79	F	8.6			17	Macrocytic	Megaloblastic	1.9	0	
8.	60	F	3.8			39.8	Macrocytic	Megaloblastic	1 0	0	
9.	85	F	8.6			14 7		Megaloblastic		0	
10.	67	F	5.7			20.8	Macrocytic	Megaloblastic		0	
11.	51	F	6.0			25		Megaloblastic	1.0	0	
12.	77	F	4.8			10.8	Macrocytic	Megaloblastic		0	
13.	59	M	7.9		4000	20	Macrocytic	Megaloblastic	3.→17.8	0	Ca Prostate
14.	64	M	5.7		1600	19			5%	0	
15.	69	F	8.7						1.9	0	Ca Colon
16.	84	M	8.7			6	Macro	Megalo	1%	0	
17.	47	F	4.2		2700		+	+	None	No	
18.	50	F	6.3		4100	10	+	+	1.2	No	
19.	64	F	4.2		1900	23	+	+		No	
20.	89	M	3.6		4000	22	+	+	1	No	
21.	75	M	6.5		3300		+	+	1.2	No	
22.	79	F	9.3				+	None	1	No	
23.	82	M	3.7		2800	2				No	PA in relapse monocytic leukemia
24.	83	M	9.9						1.6	No	
25.	78	F	5.9			19	+	+	1	No	Gastric polyp
26.	58	F	4.0			32	+	+	1	No	
27.	65	F	5.8			9	+		1.8	No	
28.	69	F	3.5			19	+		3%	No	
29.	83	F	4.2			19	+	+		No	Chronic lymphatic leukemia
30.	78	F	3.6			10		+	1 5%	No	
31.	60	F	2.9			9	+	None		No	
32.	79	M	5.8		4000	18			3%	No	
33.	63	M	4.3			21	+	+	None	No	
34.	70	F	6.0				+	+		No	
35.	53	F	4.6			13	+	+		No	
36.	60	F	5.6			20	+	+		No	
37.	79	F	4.0		2800	15	+	+	2%	No	
38.	77	F	5.5			28	+	+		No	
39.	33	F	6.1			28				No	Hypothyroid
40.	81	M	4.2		3200			+		No	Ca Prostate
41.	77	M	5.6			12.6	+	+		No	
42.	60	F	4.9		2800	24	+	+		No	
43.	74	M	5.7			16	+	+	1.3%	No	
44.	63	M	8.1				+	+		No	ASHD
45.	83	M	7.6				+	+	1%	No	Mult. myel.
46.	67	M	6.0			14%	+	+	1%	No	Gastric po
47.	81	M	7.1			24.8	+		1%	No	
48.	72	F	7.5			12.0	+		3%	No	Hypothyroid

presently falling, the reported incidence of pernicious anemia has remained constant. In studying the etiologic factors in cancer of the stomach in England, Maddock reported the following:[27]

1) The mortality for persons with pernicious anemia was the same as for the general population.
2) In comparing two endemic areas, one having a high incidence of stomach cancer, the other with an average incidence, the incidence of pernicious anemia in the two areas was the same.

He therefore concluded that statistically the two diseases do not seem to be related. In our study of 81 patients with pernicious anemia over a seven-year period there were no stomach cancers noted. It would seem that if the two diseases were closely related, and that if there is in fact an almost twenty percent increase over the expected incidence of stomach cancer, our series would also bear this out, especially since the average age of our patients was 74 years. The fact that our series is devoid of cancer of the stomach, the fact that the incidence of cancer of the stomach is declining while the incidence of pernicious anemia is relatively constant, and the fact that the only recent study of these two diseases shows no correlation, raises the question whether patients with pernicious anemia actually have an increased incidence of cancer of the stomach.

It was initially suggested by Rigler that patients with pernicious anemia should have annual radiographic stomach examinations, but this was found to be impractical and has been generally discarded.[28,29,30] The incidence of carcinoma of the stomach in persons over 50 years of age, between 1953 and 1964, at the Cancer Detection Center of the University of Minnesota, was one positive examination per 1,900 examinations, and the incidence continues to decline.[31]

Treatment[1,5,32]

The treatment of pernicious anemia is the administration of vitamin B_{12}. Dosage schedules are as varied as the clinicians treating this disease; as little as 1 mcg. of B_{12} per day can bring about clinical recovery.[22] Treatment, however, should attempt to restore the body stores of B_{12}, in addition to inducing a clinical response. The average deficit in a person with pernicious anemia is about 2,000 to 3,000 mcg. An additional consideration in treatment should be the oral administration of iron, especially if the iron stores are low. As one starts to convert from a megaloblastic to a normoblastic marrow, initially the hemoglobin may fall slightly. As effective erythropoiesis is attained, large amounts of body iron are needed for red blood cell production. Low available iron may decrease the response. There are oral forms of vitamin B_{12} with or without intrinsic factor; however, the mainstay of therapy remains parenteral administration. Since the basic defect in pernicious anemia is permanent, maintenance therapy on a regular schedule is necessary.

Case Report

Case 1

A 56-year-old white female of German-English descent was admitted to the hospital on January 14, 1968, as a disposition problem. She had no specific complaints other than muscle aches and generalized weakness. She had not been strong enough to leave her apartment for three weeks, and for one week was confined to bed due to profound weakness.

On admission the patient was noted to be somnolent, confused as to time and place, and appeared older than her stated age of 56. She had blue eyes and white silky hair, and her skin had decreased turgor, with a yellow tinge. There was minimal periorbital edema. Position

and vibration sense was poor. A faint systolic ejection murmur was noted, and her liver was palpable 3 to 4 cm. below the costal margin and was not tender.

Hospital Course

On admission her hemoglobin was 2.6 gm %, RBC 610,000, WBC 4,500, with a normal differential, and a platelet count of 15,000. The peripheral blood smear showed macrocytosis, and moderate numbers of six-lobed neutrophils were present. The diagnosis of pernicious anemia was suspected, and due to her low hemoglobin two units of whole blood were given slowly, bringing her hemoglobin up to 4.4 gm%. The next morning her strength was slightly improved, but her sensorium was still clouded.

Laboratory Findings

Chest film: Cardiac enlargement. Stool guaiacs negative throughout her course. VDRL negative. Blood chemistries on admission revealed the following abnormalities: K = 3.0, Cl = 97, albumin = 3.5, total bilirubin 1.6, cholesterol 112. PBI 6.1. Shilling test showed the following:

a) without intrinsic factor
urine excretion at 24 hours 3.7%
blood 1.62 mg/ml (normal 4.8 ± 1.6)

b) with intrinsic factor
plasma 0.238%/1% body weight
(normal 0.18 – 1.8%)

Serum Iron 245 mcg %
Iron Binding Capacity 263
% Saturation 93%

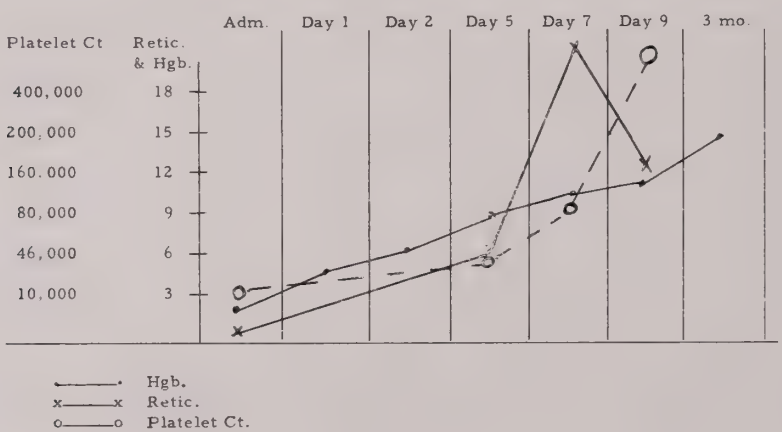
Gastroscopy and X-ray Findings

Atrophic gastritis, with a small polypoid lesion in the mid-stomach. Stomach x-rays showed a normal mucosal pattern with no gross abnormalities. There was a small hiatus hernia present with some reflux. The polypoid lesion noted on gastroscopy was not seen.

Bone Marrow

Hyperplastic marrow with no marrow fat. Sheets of megaloblasts were noted. There was no stainable iron seen.

On the fifth hospital day the patient was more alert and oriented. Her improvement was progressive and she was discharged on the 11th hospital day.



Case 2

A 79-year-old white male was admitted with a three-month history of progressive weakness. Hemoglobin in 1961 was 11.0–13.6 gm%.

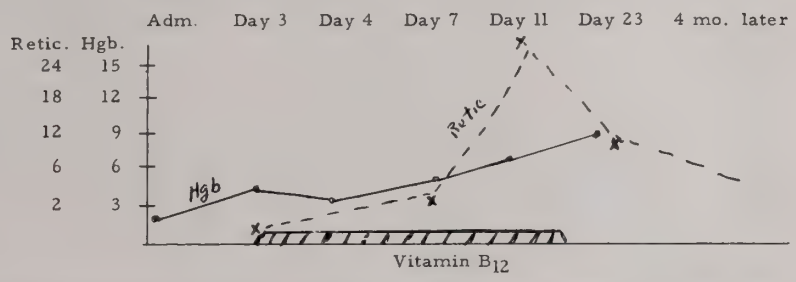
Physical Examination

Cachectic-appearing, confused white male with sallow yellow skin. There was bilateral axillary adenopathy. The chest was clear to ascultation. There was a Grade II systolic ejection murmur at the left sternal border. The liver was enlarged about 4 cm. below the costal margin and non-tender.

Laboratory Findings

Admission

Hgb. 2.9 gm%
Hct. = 9%
RBC 810,000 million
WBC 1,500 with 38% PMN's and 61% lymphocytes
Platelets = 10,000
Serum iron 186 mcg%
Iron binding capacity 212
% Saturation 88%
LDH 2713 units
PBI 5.5 mcg%
Schilling test: urine excretion 0.42% in 24 hours
Serum B_{12}—non-detectable
Total bilirubin 1.6 mg%
Coombs—negative
Gastric analysis—no free acid
Bone marrow—megaloblastic changes noted, with decreased iron stores.



The patient was treated with B_{12} and iron and responded slowly. He now has a normal hemoglobin, is oriented, and appears to be in normal health.

References may be secured from the Grand Rounds Editor.

Mirabile Dictu*

Sir Hans Sloane, who saved the Chelsea Physic Garden for the Apothecaries and Virginia, was the first physician to be made a baronet. He was a founder and later President of the Royal Society. . . . He was also for many years President of the Royal College of Physicians.

Sir Hans, like many doctors, was passionately interested in curiosities. He was particularly fond of giants. He studied their bones. There was the shin-bone of the "noble and puissant lord, the Chevalier Ricon de Vallemont." This was over four feet long, so the Chevalier must have been more than 17 feet tall. There was the giant Bucart, who was 22½ feet high according to similar calculations. Better still was Theutobochus Rex, a skeleton disinterred in 1613 and measuring 25 feet. Sir Hans concluded sadly that pretty well all these bones belonged to whales, elephants, mastodons and other animals.

Later students have taken the same view. As measurements have become more precise giants have become less gigantic. According to a nice calculation Adam was 123 feet high and Eve 118 feet, which suggests that the serpent must have been something out of this world.†

*See Test Your Word Score, Page 1583.
†Harvey Graham: A Doctor's London, 1952.



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Dermatology

Alopecia Areata

ALOPECIA IS a term derived from the Latin word alopex, meaning fox. This animal is known to suffer mange with resulting bald areas. Areata simply means *limited* or *circumscribed area.*

Alopecia areata is one of the most common types of hair loss seen by the physician. The cause is unknown. From time to time various factors have been implicated, such as dental infections, errors in visual refraction, endocrine dysfunction, toxins, and direct contagion. Currently, the most popular concept is that of an emotional disturbance underlying alopecia areata. As yet none of these possibilities has been proved.

In most instances the diagnosis is easy, as the disease is characterized by one or more circumscribed areas of hair loss (Figure). The disorder is most frequently noted on the scalp, although any hairy area may be affected. Several descriptive terms are used with respect to the extent of the process. Alopecia totalis refers to involvement of the entire scalp, while alopecia universalis denotes the loss of all body hair. Alopecia areata may occur at any age, although it is most frequent during the first to fourth decades. The disease has been noted in all races and shows approximately equal sex distribution. At times this condition has been observed in several members of the same family. In these familial cases inheritance appears to be dominant with incomplete penetrance.

Clinically, the bald areas develop rapidly (within several days). Usually only one area of hair loss is noted at first, though on close inspection numerous



Figure

small areas may be present. There is no site of predilection; vertex, parietal, occipital and temporal regions may all be affected. As a rule, the process does not begin at the margin of the scalp. The area of hair loss enlarges by peripheral extension, and new areas may appear which then enlarge and may join the other areas, resulting in an irregular pattern. The skin in the affected areas is smooth and glossy. While sensation and/or redness is often noted, atrophy does not occur. Centrally in the areas of baldness no hair is visible; however, at the periphery one sees short hairs which are atrophied at their proximal portion while thickened and dark distally. These are called exclamation point hairs and are of diagnostic importance. When these hairs are seen at the periphery of a patch of alopecia it is evidence that the process is extending. In addition, longer hairs in the vicinity of the involved area frequently come away with gentle pulling.

At times nail changes may occur with alopecia areata, such as pits, ridges, furrows, and loss of the nail itself. Other rare findings associated with this condition include intestinal polyposis, thyroid disease, scleroderma and vitiligo.

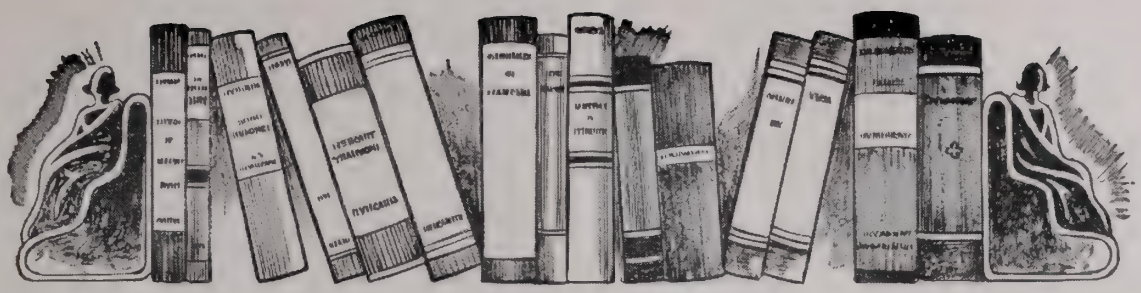
Differential diagnosis is usually not difficult. However, at times several other disorders must be brought under consideration. Non-inflammatory ringworm of the scalp may resemble alopecia areata. In this affection one usually sees scaling and some degree of erythema, which is absent in alopecia areata. Occasionally, Wood's light examination culture and microscopic study of the hairs must be made to differentiate the two disorders. Impetigo or other bacterial infections may result in localized areas of hair loss; here inflammation and crusting are present along with prompt regrowth of hair after the process is controlled. Trichotillomania (self-inflicted removal of hair) usually does not show total baldness in the involved areas, and many short broken hairs are commonly present. The cicatricial alopecias such as lupus erythematosus, folliculitis decalvans and pseudo-palade all show atrophy as well as varying degrees of inflammation. Syphilitic (moth-eaten) alopecia may cause difficulty; here history, general physical examination and serologic tests are important in the differentiation from alopecia areata.

Prognosis in alopecia areata is not always easy. If the areas of involvement are few, regrowth may occur within four to 12 months. If the process is extensive, such as alopecia totalis, or if there are numerous areas, chances for regrowth are less favorable. Also, the longer the disease remains active, the less favorable is the prognosis. Of those patients recovering approximately 25 to 30 percent will have recurrences; the more frequent these recurrences, the poorer the prognosis.

Treatment of alopecia areata is generally unsatisfactory. Therapy consists of stimulatory measures such as strong ointments and ultraviolet radiation. These measures are probably based upon the concept that stimulation of hair follicles in certain animals has been proven to induce hair growth, but no such proof exists for the human hair follicle. General supportive measures, as well as topical and intra-lesional steroids, may be used. Steroids may induce hair growth, but when they are discontinued, the hairs will often be shed. This disorder warrants further study concerning etiology as well as treatment.

Willard C. Peterson, Jr., M.D.
Minneapolis, Minnesota

No man is a good physician who has never been sick.—Arabian Proverb



Book Reviews

Books are like windows of a great tower. They let light in.—William Stidger

CURE FOR CANCER. A NATIONAL GOAL. Solomon Garb, M.D., Professor of Pharmacology, and Associate Professor of Community Health and Medical Practice, University of Missouri, School of Medicine, Pages 303, Springer Publishing Company, Inc., New York, N. Y. 1968.

Doctor Garb analyzes current cancer research. It is time, he says, to direct our resources toward a national goal aimed at cure or control of cancer, particularly since the death rate has risen in spite of the availability of many anti-cancer drugs.

The author comments upon the organization and budgeting of a national cancer research program, the nature of cancer, screening of anti-cancer materials, vaccines against cancer, spontaneous, induced, and transplanted cancer, genetic and molecular approaches to malignant neoplasms. Reasons are presented for a more intense study of plant material, bacteria and bacterial products, as well as sources from the sea such as extracts from the common clam. Surgical and radiotherapeutic measures are discussed. It is pointed out that cancer does not tend to regrow around the suture line when iodized sutures are used; also that radiation treatment cures some cancers, but that how this happens is still conjectural. While Burkitt's lymphoma and certain leukemias in children seem to be virus-linked, there is as yet no data showing that viruses are causally related to other human cancers.

The opinion is expressed that valuable contributions in cancer research can be made by veterinarians, pharmacists, dentists, and general biologists.

In the chapter "Leukemias and Ascorbic Acid" Dr. Garb advances the postulate that "some of the more distressing and dangerous symptoms of leukemia may be due to a relative deficiency of ascorbic acid (vitamin C)." While the ascorbic acid body level in health is about four grams, and one gram of this is held by the leukocytes tissue, subsaturation may result from a large volume of leukemic cells hoarding the vitamin and thus giving rise to symptoms resembling scurvy. Up to nine grams may be needed to establish a normal ascorbic acid balance. Barkham and Howard (Biochem. J. 70:163, 1958), for example, had to give approximately 15 grams of vitamin C to produce saturation. Whether ascorbic acid balance enhances the effectiveness of chemotherapeutic agents should be vigorously studied. This reviewer has observed beneficial effects from large daily doses of four to five grams of ascorbic acid in leukemic states complicated by scurvy.

Because Dr. Garb has packed a wealth of provocative data into 303 pages, it should be worth while for cancer researchers and allied scientists to read the booklet from cover to cover.

Emil Maro Schleicher, Ph.D.
Minneapolis, Minnesota

INTERNAL MEDICINE BASED ON MECHANISMS OF DISEASE, Peter J. Talso and Alexander P. Remenchik, Editors; C. V. Mosby Company, 1968; 797 pages; Price: $17.50.

Thirty-one contributing authors have written chapters in the first edition of this textbook of internal medicine. Although the title would suggest that the text is devoted to the abnormal physiology of disease, the book is mainly devoted to clinical aspects of diagnosis and treatment of the major diseases encountered in internal medicine. The first two sections of the book consisting of thirteen chapters are devoted to a discussion of internal medicine as a science and an art and the basic mechanisms of selected important disease states which apply in a number of specific diseases. The remainder of the book is devoted to discussion of the clinical aspects of diagnosis, therapy, and pathophysiology of the major diseases of the heart and blood vessels, the respiratory tract, the digestive system, and the endocrine system. In the last section the clinical aspects of diseases of the kidney, blood, musculoskeletal system and neurological and psychiatric disorders are presented.

The text is clearly written and reasonably well illustrated and contains key references to the medical literature for readers who wish to go into each subject in greater depth. Although the discussions in the various sections might be disappointing to the investigator in the field and the highly trained specialist, the material presented is quite comprehensive and will be useful to medical students, interns, residents, and general internists in the management of most problems encountered in the practice of internal medicine.

The book is recommended to medical students, house officers and physicians practicing general internal medicine as a good, well written text which will be useful along with one of the larger more comprehensive general textbooks of internal medicine.

Alvin L. Schultz, M.D.
Minneapolis, Minnesota



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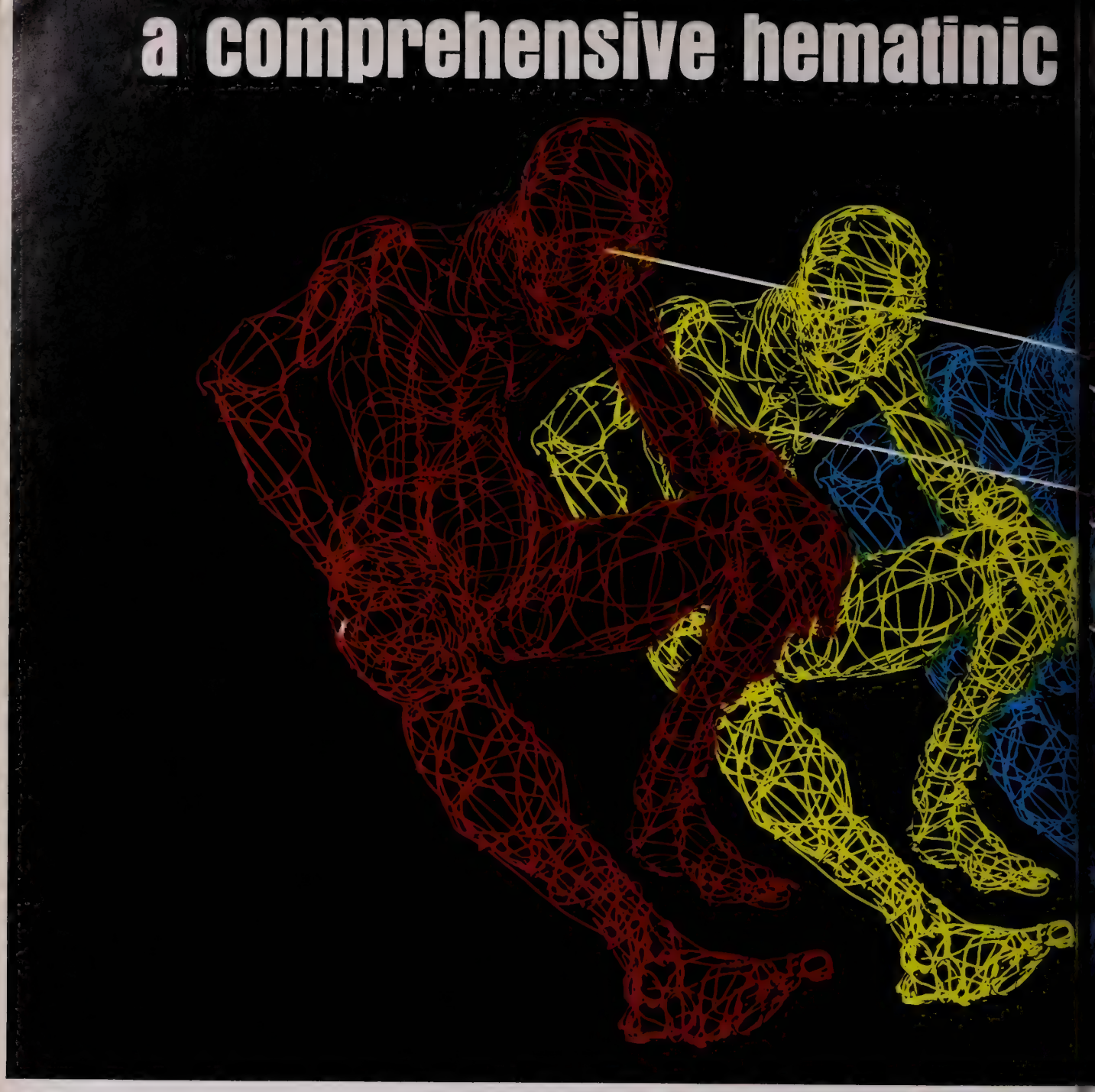
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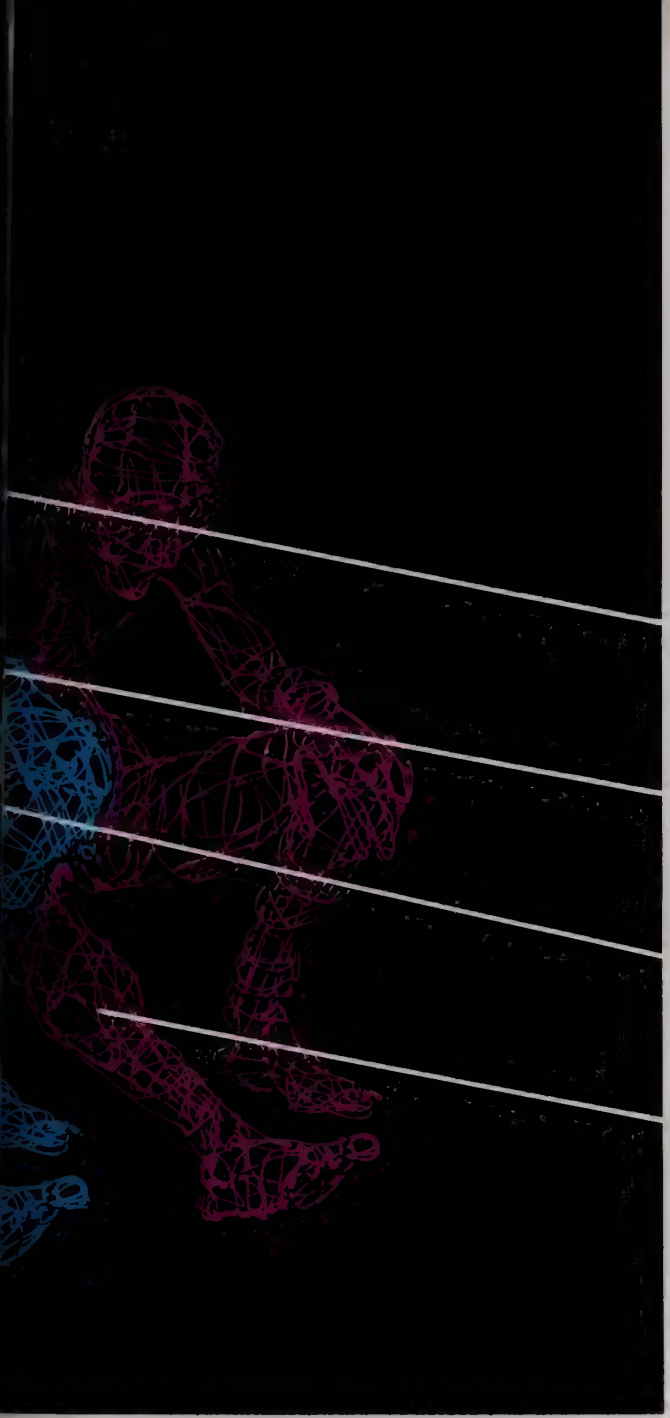
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Special Article

Studies on the Circulation of Dogs

Following the Injection of Contrast X-ray Media*

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R. FELIX, M.D.*
N. DRAZNIN, M.D.*
Bonn, West Germany

A SERIES OF studies on human blood circulation after the peripheral injection of contrast X-ray media[9] revealed obvious changes of the blood pressure, the stroke volume, and the minute volume of the cardiac output.

In continuation we now report about studies done on anesthetized dogs. Pressures were determined in the aorta, in the pulmonary artery, and in the left atrium. Heart rate was recorded after the injection of 76% Urografin† and Urovison‡ into the right atrium in the same manner as in the selective dextrocardiography. Assuming that this type of injection produces a higher concentration of dye in the heart than when given peripherally, more obvious reactions should be expected.

Technique

We evaluated the electronically determined median pressure values§ and the heart frequencies as recorded by the electrocardiographs‖ on seven mongrel dogs, 18 to 25 kg. The dogs were sedated with Combelen+ subcutaneous, 1 mg/kg bodyweight, and after 20-30 minutes, 35 mg/kg Nembutal¶ intravenously.

Pressure in Aorta and Pulmonary Artery

Through an incision in the groin a catheter was inserted into the femoral artery to measure the pressure in the aorta, and another

*From The Department of Experimental Surgery of the Surgical Clinic (Director: Professor Dr. A. Gütgemann).
The Institute of Radiology and Radiotherapy. (Director: Professor Dr. P. Thurn). University of Bonn, Federal Republic of Germany.
The senior medical students H. Becker and H. Seboldt and the technical assistants Miss H. Küehl, Mrs. J. Sieger and Mrs. W. Pöehler helped in these studies.
German original text: to be published in Zeitschrift für Kreislaufforschung. Dr. Dietrich Steinkopf, publisher, Darmstadt.
†In 1 ml 0.1 g Sodium- and 0.66 g Methylglukaminsalt of N,N'-Diacetyl-3,5-Diamino-2,4,6,-Triiodo-benzoic acid (Schering, AG., Berlin.)
‡In 1 ml 0.4 g Sodium- and 0.18 g Methylglukaminsalt of N,N' - Diacetyl-3,5-Diamino -2,4,6,- Triiodo-benzoic acid (Schering, A.G., Berlin.)
§Fritz Hellige & Co. GmbH, Elektomanometer Ma-88 G and Fritz Schwarzer GmbH, Müenchen, Messverstäerker TV 540.
‖Mela KG, Müenchen, Monitor P 2.
+Farbenfabriken Bayer A. G., Leverkusen.
¶Abbott GmbH, Frankfurt/M.

catheter was passed through the femoral vein for the injection of dye into the right atrium. A catheter was then inserted through the right external jugular vein into the pulmonary artery for the purpose of determining the pressure. Thereafter a thoracotomy was performed and a catheter inserted through the left auricle into the left atrium. In order to prevent the lodging of the tip of the catheter against an atrial wall the catheter was fixated in the wall of the thorax. The correct position of the catheters was checked by radioscopy.

All values were recorded two to three minutes before and continuously for 10 minutes following the injection* of the dye into the right atrium. Normal saline or Ringer's solution was used in the control series.

Rebreathing

Some of the experiments were done in combination with unilateral rebreathing, in the same way as in certain pulmonary function studies[3]. After introduction of a Carlens-double lumen intratracheal tube we connected one tube with a five-liter-sized bag, in which one lung was rebreathing. This was done to check if there was a correlation between the increased pulmonary circulatory load and the possible qualitative or quantitative reactions of the general circulation in response to the injection of dyes. The timing of the dye injections and of the normal breathing and unilateral rebreathing was done in varied sequences.

Results

Because there were no differences found when the dyes or the Ringer's solution were injected under normal or unilateral breathing, the values obtained were treated in the same way. We took measurements at five, 15, 30, and 45 seconds after the start of the injections and thereafter every minute from one to 10 minutes. After the injection of normal saline or Ringer's solution the checking was done for five minutes because the values returned to normal in that time. In retrospect it appears that later measuring of the pressures in the pulmonary artery could have been of value.

*Elema-Schoenander AB, Stockholm. High-power injection syringe. Pressure of 1 atm/3 equals 14.69 lbs./square inch.

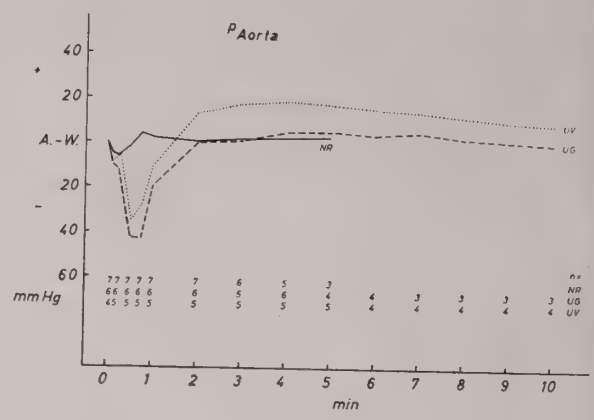


Figure 1.

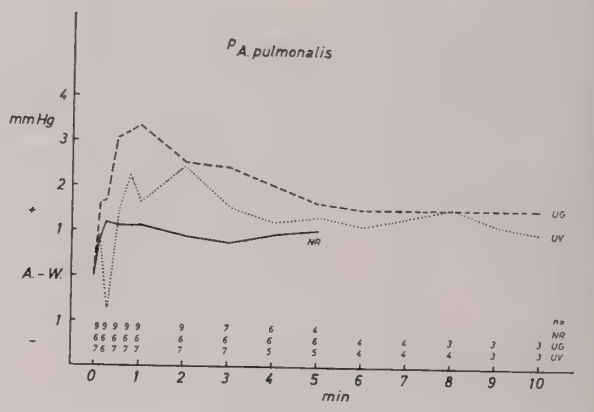


Figure 2.

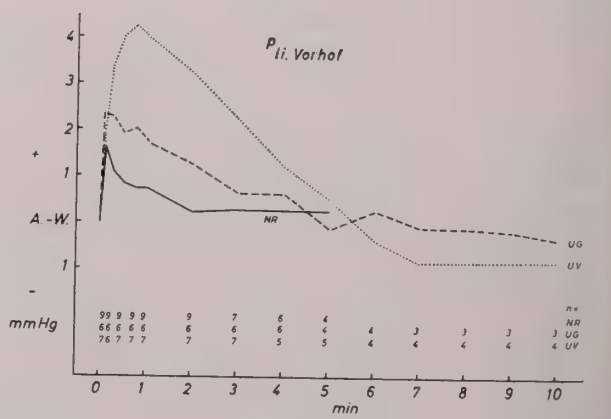


Figure 3.

Pressure Differences

Illustrations one to five show the measured values of the pressures in the aortic arteries, in the pulmonary arteries and in the left atria (Figures 1, 2 and 3). In addition, the pressure differences between the pulmonary arteries and the left atria and the heart rates are shown (Figure 4). All measured values were computed in relation to the starting values, not the absolute values, since there is less straying. This is particularly helpful when we are measuring the pulmonary artery and left atrium pressures, since the absolute values cannot be measured exactly the same way from one animal to the next because of technical difficulties. On one occasion we also checked the pressure in the caval vein. During the injection the pressure went up about 3 to 5 mm Hg, but thereafter no further changes were observed. Therefore further measurements were not taken.

*See Test Your Word Score Page 1583.

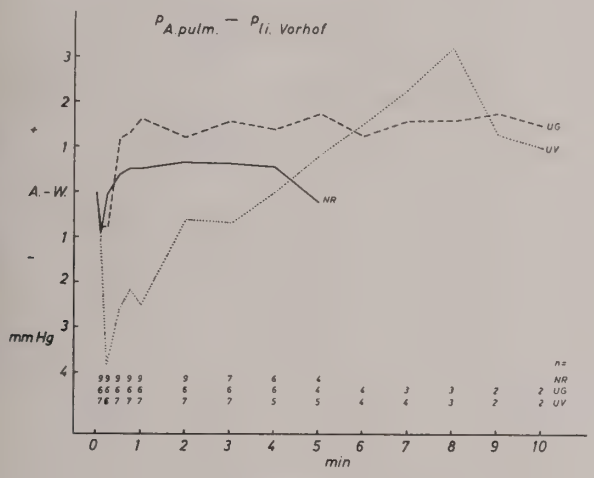


Figure 4.

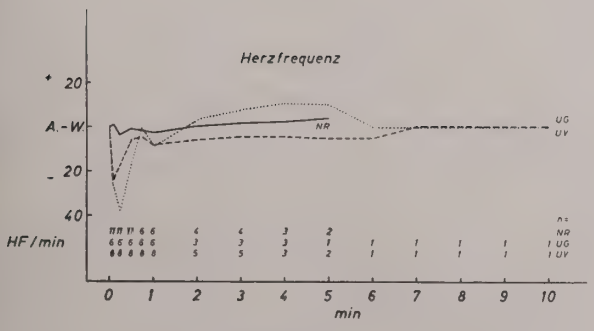


Figure 5.

Mean Values

Table 1 shows the mean values and the observed straying. For clearness we have not included the straying into the curves of the illustrations. Significant differences are reported in Table 2 with corresponding error possibility "p." Because of technical difficulties with the heart rate integrator we were unable to follow the injection of the one dye for the full 10 minutes, the other for only five minutes (Figure 5). The measured values are included in this illustration, but not in Table 1, since the statistical evaluation of the straying is not available.

Discussion

Contrary to the almost absent changes in the pressure of the aorta and the heart rate after injection of saline or Ringer's solution there are marked changes after the injection of Urografin and Urovison. After injection of these, a considerable drop in the aortic pressure and an increase of the pressure in the pulmonary artery and the left atrium occur, combined with a decreased heart rate.

According to these findings there were no changes caused by the sudden increase in volume (40 ml) in the right atrium after injection of normal saline or Ringer's solution; consequently it seems reasonable to presume that the reaction is not started by the volume but by the chemical constitution of the dye. Possibly a slight acidity may be of importance since the pH of Urografin is 7.15 and that of Urovison is 6.38.

Viscosity

The higher viscosity of the dyes has been said to have an influence on the circulation.[5] But the absolute viscosity of blood in vivo is 2.70 centipoise*.[11] The viscosity of Urografin 76% at 37° C is about 8.50 centipoise and that of Urovison about 3.30 centipoise. Urografin injection could therefore show some influence on the circulation, but probably not Urovison. Because the reactions after Urovison are occasionally more pronounced than after Urografin, an influence of the viscosity does not appear to be likely. Possibly the higher acidity may be the reason for the stronger

TABLE I

Mean Values and Amount of Stray at the Times of Measuring in Relation to the Starting (Pre-Injection) Values

Time after Injection	Injected Substance	Aortic Pressure in mm Hg	Pressure in the Pulmonary Artery mm Hg	Pressure in left Atrium mm Hg	Pressure Difference Pulm. Art. vs. lt. Atrium mm Hg	Heart Rate/min
5″	NR	— 4.6± 4.6	+ 0.7± 0.3	+ 1.6± 1.2	— 0.9± 0.5	+ 1.4± 3.7
	UG	—10 3± 4.8	+ 1.6± 0.3	+ 2.3± 1.0	— 0.8± 0.7	—22.5±14.4
	UV	— 8.8± 7.3	+ 0.9± 0.7	+ 1.9± 0.7	— 1.0± 0.9	—25.6±12.3
15″	NR	— 6.0± 3.3	+ 1 2± 0.5	+ 1.2± 0.5	— 0.1± 0.6	— 3.2± 1.0
	UG	—12.5± 5.6	+ 1.7± 0.4	+ 2.3± 0.8	— 0.8± 0.5	—16.5± 4.9
	UV	— 6 0±11.8	— 0.7± 0.6	+ 3.4± 1.1	— 4.1± 1.4	—37.6±12.8
30″	NR	— 1.7± 3.1	+ 1.2± 0.7	+ 0.8± 0.3	+ 0.4± 0.4	— 1.4± 0.6
	UG	—42.5± 6.3	+ 3.1± 0.5	+ 1.9± 0.8	+ 1.2± 0.8	— 5.8± 4 8
	UV	—35.0± 2.7	+ 1.4± 1.0	+ 4.0± 1.0	+ 2.6± 1.6	—17.3±10.5
45″	NR	+ 3.3± 5.0	+ 1.2± 0.6	+ 0.7± 0.4	+ 0.5± 0.4	— 2.0± 1.6
	UG	—42.5± 4.2	+ 3 2± 0.6	+ 2.0± 0.6	+ 1.3± 0.7	— 5.0± 3.7
	UV	—28.0± 5.2	+ 2.2± 0.9	+ 4.2± 1.7	— 2.2± 1.8	— 0.9± 7.9
1′	NR	+ 2 6± 1.6	+ 1.2± 0.7	+ 0.7± 0.4	+ 0.5± 0.3	— 2.8± 2.5
	UG	—20.0± 4.5	+ 3 3± 0.9	+ 1.7± 0.8	+ 1.6± 0.9	— 8.2± 2.6
	UV	—11.0± 9.9	+ 1.6± 0.9	+ 4.1± 1.8	— 2.5± 2.0	— 8.6± 8.9
2′	NR	+ 0.9± 1.4	+ 0.9± 0.4	+ 0.2± 0.3	+ 0.7± 0.4	+ 0.5± 0.5
	UG	— 0.8± 5.2	+ 2.5± 0.5	+ 1.3± 1.0	+ 1.2± 1.2	— 6.0± 2.1
	UV	+13.0± 4 4	+ 2.4± 1.0	+ 3.2± 1.0	— 0.6± 1.1	+ 3.0± 8.4
3′	NR	+ 2 2± 1.0	+ 0.7± 0.6	+ 0.3± 0.2	+ 0.6± 0.5	+ 1.8± 1.2
	UG	+ 0.8± 4.7	+ 2.4± 0.4	+ 0.7± 1.4	+ 1.6± 1.1	— 4.3± 6.8
	UV	+17.0± 2.6	+ 1 5± 0.7	+ 2.2± 0.4	— 0.7± 0.5	+ 7.4± 8.2
4′	NR	+ 2.6± 1.1	+ 0.9± 0.7	+ 0.3± 0.2	+ 0.6± 0.7	+ 2.3± 1.5
	UG	+ 5.0± 3.9	+ 2.0± 0.4	+ 0.7± 1.2	+ 1.4± 1.3	— 4.3± 6.8
	UV	+18.0± 2.0	+ 1.2± 0.9	+ 1.2± 0.6	0.0± 1.0	+10.7± 6.4
5′	NR	+ 3.3± 1.0	+ 1 0± 0.7	+ 0.3± 0.3	— 0.3± 0.5	+ 3.5± 1.5
	UG	+ 5.5± 4.2	+ 1.6± 0.5	— 0.1± 1.3	+ 1.8± 1.4	.....
	UV	+17.0± 1.2	+ 1 3± 0.6	+ 0.5± 0.9	+ 0.8± 1.5	+10.0±15.0
6′	NR	.....	.....	.....	.....	.....
	UG	+ 3.8± 4.3	+ 1.5± 0.5	+ 0.3± 0.8	+ 1.3± 0.8	.....
	UV	+15.0± 2.0	+ 1 1± 0.4	— 0.4± 0.9	+ 1.5± 1.0	.....
7′	NR	.....	.....	.....	.....	.....
	UG	+ 5.0± 5.8	+ 1.5± 0.8	— 0.1± 0.9	+ 1.6± 0.8	.....
	UV	+14.3± 1.4	+ 1 4± 0.6	— 0.9± 1.2	+ 2.3± 1.2	.....
8′	NR	.....	.....	.....	.....	.....
	UG	+ 2.7± 5.0	+ 1.5± 0.9	— 0.1± 0.6	+ 1.6± 0.5	.....
	UV	+12.0± 3.4	+ 1 5± 0.6	— 0.9± 1.2	+ 3.2± 1.3	.....
9′	NR	.....	.....	.....	.....	.....
	UG	+ 2.3± 5.4	+ 1 5± 0.9	— 0.2± 0.7	+ 1.8± 0.8	.....
	UV	+10.5± 4.2	+ 1.2± 0.6	— 0.9± 1.2	+ 1.3± 0.7	.....
10′	NR	.....	.....	.....	.....	.....
	UG	0 0± 5.8	+ 1.5± 0.8	— 0.3± 0.8	+ 1.5± 1.0	.....
	UV	+ 9.5± 4.9	+ 1.0± 0.5	— 0.9± 1.2	+ 1.0± 0.5	.....

NR = 0.9% NaCl- oder Ringer solution
UG = Urografin 76%
UV = Urovison

effects of Urovison.

Bezold-Jarisch Reflex

One may think about the possible appearance of a Bezold-Jarisch-reflex,[2,7,8] caused by reaction of chemical receptors in the left ventricle. In favor of this is the earlier onset of the reaction which occurs two to three seconds after the injection. The circulation time in the cat from the right atrium to the aortic bow is about three to four seconds.[8] Assuming a similar situation in the dog the reaction could be started in the left ventricle, but surgical section of the bilateral vagus nerves at the neck did not change the circulatory reaction of the dye injections; therefore our previously expressed opinion[9] about the presence of a Bezold-Jarisch reflex does not seem to be substantiated. Obviously the circulatory reaction originates locally by direct contact of the dye with the sinus node and the myocardium so that it might appear like a Bezold-Jarisch reflex.

Hypotonic Phase

After one to two minutes the depressed pressure and frequency values return to the starting point and thereafter keep rising. However, after 10 minutes the values are back at the pre-injection levels. This phenomenon might be explained by a centrally originating counter-reaction or by a direct central irritation.

The changes of the aortic pressure correspond with the findings of other examiners[1,4,10,12] and with our own findings in men.[9] We noted then a slight increase of the blood pressure two minutes after injection of Uro-

TABLE 2

Possibility of Error "p" of Significant Differences of the Results of the Three Examined Media.

Time after injection	Aortic Pressure			Pressure in Pulmonary Artery			Left Atrial Pressure		
	NR/UG	NR/UV	UG/UV	NR/UG	NR/UV	UG/UV	NR/UG	NR/UV	NR/UG
5″									
15″					<0.05	<0.01			
30″	<0.001	<0.001						<0.001	
45″	<0.001	<0.001						<0.05	
1′	<0.001	<0.05							
2′				<0.05				<0.01	
3′		<0.001	<0.02					<0.001	
4′		<0.001	<0.02	<0.05					
5′		<0.001	<0.05						
6′									
7′									
8′									
9′									
10′									

Time after injection	Pressure-Difference Pulmonary Artery vs. left Atrium			Heart Rate/min		
	NR/UG	NR/UV	UG/UV	NR/UG	NR/UV	UG/UV
5″						
15″		<0.02		<0.01	<0.001	
30″						
45″						
1′						
2′						
3′						
4′						
5′						
6′						
7′						
8′						
9′						
10′						

NR = 0.9% Saline or Ringer's solution, UG = Urografin 76%, UV = Urovison.

grafin, slowly decreasing to the tenth minute. Since we then checked the blood pressure with the method of Riva Rocci, we might possibly not have been able to find the drop in blood pressure during the first minute. Probably the observed time difference in the course of the reaction could be caused by the injection in a peripheral arm vein in human experiments. Also the amount of the dye injected into men was only 20 ml instead of 40 ml as used in the dogs; therefore a lesser dye concentration was present in the heart. This might also explain the less pronounced first phase, which in turn produced an earlier start of the second phase with an increased aortic pressure.

In the literature[6] two hypotonic phases are described in the aortic pressure after injection of a diazotrate in the carotid artery. We found that this phenomenon occurred only slightly and after a much shorter time than the 20 and 25 seconds described in the literature. We noted the first hypotonic phase after five seconds, the second after about 30 seconds. As this was seen only occasionally, it changes the median values in Figure 1 only slightly. The difference is probably caused by the varied sites of the injection: the contrast medium injected into the carotid artery reached the brain much earlier and in greater concentration than the dye injected into the right atrium.

The heart rate in dogs and men was influenced by the injection in the same way. The decrease in the aortic pressure and the slowing of the heart rate produce a slight stasis in the pulmonary circulation, as shown by the slight increase of the pressure in the pulmonary artery and the left atrium. While the changes in the aortic pressures are similar with the injection of Urografin and Urovison, they differ in the pulmonary artery and the left atrium. In the pulmonary artery there is a pressure increase of about 3 mm Hg one minute after the injection of Urografin. After injection of Urovison a pressure drop of about 0.75 mm Hg was noted after 15 seconds, followed later in the first or second minute by an increase of 2 to 2.5 mm Hg above the starting value. The pressure in the left atrium increases immediately after both dyes, but more with Urovison than with Urografin. After Urovison the pressure increases by 4 mm Hg maximal after one minute; after Urografin 2.5 mm Hg maximal after 15 seconds.

Hypertonic Phase

Computing the difference of the pressures between the pulmonary artery and the left atrium one notes an increase following a slight temporary decrease after 10 to 15 seconds, which does not subside within 10 minutes. The increase after Urovison starts after four minutes; the increase after Urografin after 20 seconds.

These differences between the two dyes and between the dyes and the saline solutions are not statistically valid because of the large stray deviations. But it is possible that the variations are caused by the different content of sodium and by the pH values.

The increase in the pressure differences between pulmonary artery and left atrium could be caused by an increase of the vascular resistance in the pulmonary circulation; but since we do not have cardiac output values, we cannot prove it. One would think, however, that the cardiac output probably drops with slowing of the heart rate. Decreased cardiac output in combination with increased pressure difference between pulmonary artery and left atrium would favor increased resistance of the pulmonary bed.

We have nothing to say about the resistance in the body circulation. The decrease in the difference of pressure between aorta and vena cava parallels the decrease of the heart rate, which probably causes a decrease of the cardiac output. But since we did not have the equipment to measure it, we cannot make any positive statements.

There are reports in the literature[6] about a decrease in the arterial resistance in an extremity after injection of a Diazotrate into the femoral artery. The cerebral arteries, on the other hand, contract. Therefore an increase in the resistance of the pulmonary circulation does not seem to be impossible. Such a phenomenon could be explained by multiple sites of reaction of the injected dyes: namely the heart, the blood vessels, and the cerebral centers of the vasoregulation.

There are reports about studies of the action of Urografin on the brain.[5] We cannot exclude the possibility that the changes in the pulmonary circulation are caused by central

action, but the primary hypotonic and bradycardiac phase is not caused centrally.

During the present studies we encountered the following complications: one dog died immediately after the injection of normal saline, and another dog developed an absolute arrhythmia due to atrial fibrillation.

This did not change spontaneously, however, but converted to sinus rhythm after injection of the contrast medium. In addition we noted two other occurrences of ventricular fibrillation after the dye injections, but they lasted only about 20 to 30 seconds and disappeared spontaneously. These difficulties were probably caused by irritation of the heart by the three indwelling catheters.

In the case of the dog that died a possible sensitivity of the sinus node to stretching may have been instrumental. The saline injection was the first injection given this dog. The atrial fibrillation could have been similarly caused. The ventricular fibrillation due to an irritation of the ventricular pathways is probably chemically caused.

Translated by: Heinrich H. Dierker, M.D.

Since all solutions were warmed to 37° before the injections no temperature effects could be expected.

Summary

Seven anesthetized dogs (Combelen-nembutal) were injected with 76% Urografin and Urovison through a catheter into the right atrium. The blood pressures in the aorta, the pulmonary artery and the left atrium in addition to the heart rate were measured continuously and simultaneously. The reactions caused by the two different contrast media were quite similar, but different findings were noticed in the left intra-atrial pressures and in the pressure differences between the pulmonary artery and the left atrium. For comparison, injections of normal saline and Ringer's solutions were given. There were significant differences in the action between the saline and the contrast media at different times. The reactions are probably caused by direct action on the sinus node and the myocardium, followed by action of the injected dyes at the cerebral centers.

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Abdominal Syndrome

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Meprobamate: Drowsiness may occur and can be associated with ataxia; the symptom can usually be controlled by decreasing the dose, or by concomitant administration of central stimulants. Allergic or idiosyncratic reactions: maculopapular rash, acute nonthrombocytopenic purpura with petechiae, ecchymoses, peripheral edema and fever, transient leukopenia. A case of fatal bullous dermatitis, following administration of meprobamate and prednisolone, has been reported. Hypersensitivity has produced fever, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, stomatitis, proctitis (1 case), anaphylaxis, agranulocytosis and thrombocytopenic purpura, and a fatal instance of aplastic anemia, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity, usually after excessive dosage. Impairment of visual accommodation. Massive overdosage may produce drowsiness, lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse.

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Review

Causation as It Relates to Cancer Theory*

As evidence on the causes and nature of cancer rapidly increases, confusion seems to magnify rather than diminish. There are primarily two camps of cancer theorists: a genetic group that maintains that cancer is caused by a genotypic change, and a biochemical group that maintains that cancer is caused by a metabolic change. Much of the debate is due not to conflicting evidence but to failure to determine what is meant by "cause."

Etiology

So far as cancer is concerned, it is possible to distinguish four levels of causation:

1. A primary level which is the level of first cause (initiating cause). To say that something is the cause of cancer at this level means that it initiates the process.
2. A secondary level which relates to neoplasm continuity. To say that something is the cause of cancer at this level means that it is responsible for continuation of the process.
3. A tertiary level which relates to neoplastic properties. To say that something is the cause of cancer at this level means that it accounts for the tumor properties.
4. A quaternary level which relates to host response. To say that something is the cause of cancer at this level means that it allows the survival of the tumor (e.g., immune tolerance).

It is obvious that these levels of causation are not independent, but that each preceding level can be said to initiate the following level. Thus radiation acts upon the genotype to produce a continuing genotypic change (cancer state) which in its turn is responsible for tumor properties which in their turn may be partly responsible for failure of the host to eliminate tumor cells.

It is principally with the first level of causation that persons are concerned when they speak of "cause," even if they are at one and the same time confusing it with another level. It is probably readily apparent that the first and the third levels are most often confused. Because the first level is of primary concern, the rest of this paper will discuss causes of cancer at this level, looking at both the genetic and the metabolic viewpoints.

The Genetic Theory

The Chromatin

There is dramatic evidence that change in genotype is related to the development of cancer. The physical counterpart of the construct genotype, the chromatin, is increased in cancer cells, replicates more frequently, and is more darkly staining. The chromosomes are often abnormal, with deviation from normal number and changes in structure, including inversions, deletions, translocations, and ring forms. These changes in turn result in abnormal mitoses and are themselves the cause of abnormal mitoses. The multiple mitotic spindles of cancer cells are almost pathognomonic of the disease.[1]

Totipotential Cell

Additional support for the genetic theory comes from studies on the totipotentiality of germ cells and early cleavage cells demon-

*Paper supported in part by Grant CH05190 to Y. Maruyama, M.D., National Cancer Institute, National Institute of Health.

strated for amphibians and other animals, including man.[2] It is possible that cancer is one genotypic expression of a totipotential cell.[3]

But most important, cancer is transmissible from mother cell to daughter cell, and so probably involves the mechanism of genetic transmission and the genotype.[4]

While the evidence on a genetic mechanism for cancer allows a number of interpretations, it is possible to draw some conclusions that are more probable than others. Thus, while genetic change cannot be said to be the initiating cause of cancer, it is a necessary change reflected in the fact that cancer is somatically transmissible. Both genotypic change and the resulting increased rate of cell division seen in some cancers increase the probability of chromosome abnormalities.

The Metabolic Theory

Lactic Acid

As with the genetic theory of cancer, there is evidence to support the metabolic theory. Cancer cells exhibit a high rate of lactate formation, even under aerobic conditions[5]; related to this is the fact that they also exhibit a decreased uptake of oxygen in the presence of all essential metabolites. There is evidence to suggest that the Krebs cycle is only partially operative in tumor cells.[6-8] The formation of lactic acid seems to take precedence over everything else.[9]

Enzymes

As further confirmation of the metabolic theory, cancer cells have been found to possess a high concentration of adenosine triphosphate hydrolytic enzymes,[1] to incorporate a greater percentage of total amino acids into nuclear proteins, and in general to have fewer special components such as enzymes.[10-13]

In considering the possibility of a metabolic cause of cancer, the following points come to mind:

1. If metabolic changes initiate the process of cancer, then they probably do so by acting on the genotype.
2. The broad metabolic changes mentioned above are probably secondary to genotypic change, because they are themselves transmissible.

Analysis

Figure 1 is an attempt to relate genotypic change to phenotypic change. It takes the form of a spiral, from which it becomes apparent that there are two groups of primary causes of cancer (in the sense of this paper):

1. Changes in the genotype which do not involve endogenous biochemical intervention, and
2. Changes produced by endogenous biochemical mediation.

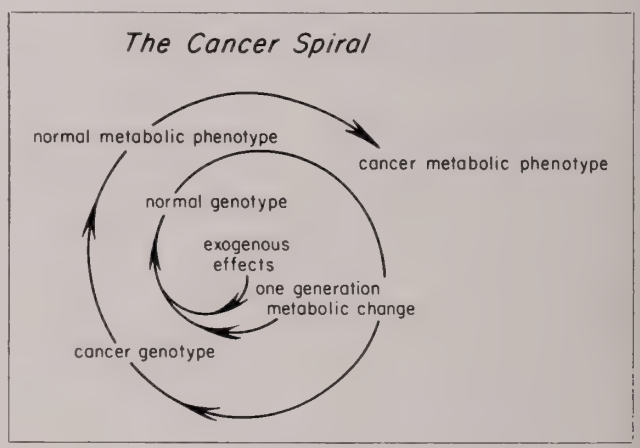


Figure 1

Both types of change will result in structural change in the cell genetic material. The structural change in turn can be considered more basically a chemical change.

A direct change in genotype seems readily possible, and there are a multitude of different effectors: radiation, drugs affecting nucleotide synthesis, incorporation of viral genes into the host genome. The change could likely involve the operon of Jacob and Monod (Figure 2). In this case, the operon might be called the cancer operon(s) and its impaired function would produce the expression of cancer. If there is a repressor associated with the operon, then: (1) the operon would produce the cancer state in the absence of this repressor, and (2) the repressor* would have to be its own template, because "one-generation biochemical effects"† produce transmissible change.

*The repressor probably acts through a substance whose manufacture it mediates.

†No mention is made of the duration of this change, which may be considerable in cells that do not have a rapid turnover, or any turnover.

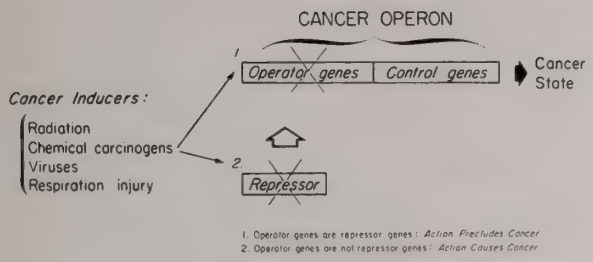


Figure 2

Now there is indeed a substance in the cell that is its own template, and that is deoxyribonucleic acid. It is therefore probable that the repressor is deoxyribonucleic acid. More directly, the repressor could be conceived as the operator gene itself. This reasoning is summarized in Figure 2.

It is therefore possible that cancer is due to a change in an operon, or more specifically in operator genes and, most specifically, in the structure of those genes, or in *base sequence*. Thus radiation, chromosomal deletion, translocation, incorporation of viral deoxyribonucleic acid, etc., alter base sequence in the operator genes and consequently destroy the inhibition of the operator, so that cancer becomes expressed.

The Special Case of the Warburg Theory

The Warburg theory is discussed separately here so that it can be related to the foregoing analysis. The Warburg theory is a metabolic theory of cancer that considers that respiration injury is the primary cause of the disease.[5] According to this theory, such injury results in the cancer cells' greater reliance on glycolysis as seen by a shift to aerobic fermentation. All the properties of cancer cells are considered to relate to this basic change. This is an extreme view only because it is posited as *the* cause of cancer. Indeed, it most certainly could be *a* cause of cancer.

If a cell requires a certain amount of energy to maintain its genetic coding, it follows that energy lack may damage that coding; it further follows that the cells that survive will exhibit a shift to aerobic fermentation as an alternative energy source making for survival. Thus Warburg's theory becomes consistent with the overall view set forth in this paper.*

*Warburg's theory as it relates to the cell grana has not been considered.

†Predoctoral Trainee, Division of Radiation Therapy, University of Minnesota Hospitals.

Summary

1. Cancer can be thought to have four different levels of causation.
2. Because cancer traits are transmissible from mother cell to daughter cell, cancer is likely to involve a change of genotype.
3. The change in genotype is mediated by a number of *primary causes* which are ultimately responsible for the presence, properties, and propagation of what is known as cancer. There is no primary cause of cancer, but there is likely only one secondary cause, or only one reason for neoplastic continuity, namely, genotypic change.
4. It is probable that changes in metabolism seen in cancer cells are due to changes in genotype. Any metabolic change that actually produced cancer would probably be masked or destroyed by the cancer metabolic phenotype. Precancer cells would be a more fruitful place to identify the existence of such changes, if such cells could be identified.

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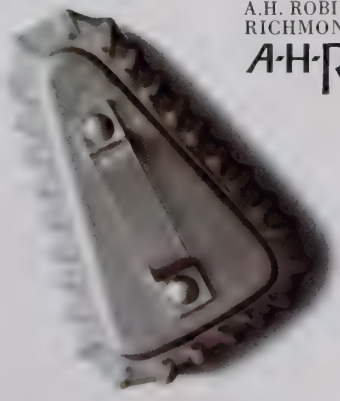
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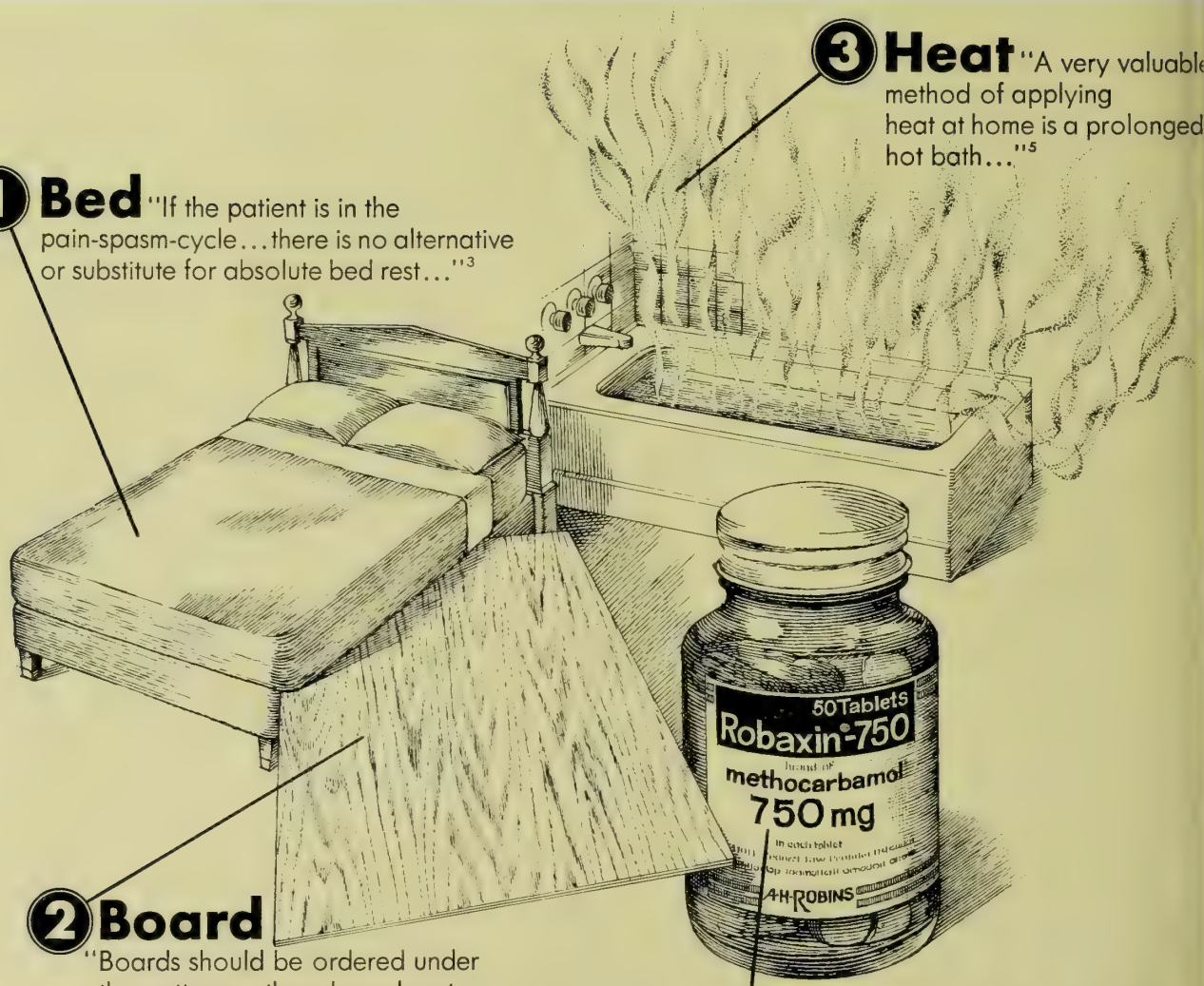
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Abstracts, Briefs and Commentaries

THE COMPARATIVE APPRAISAL OF THE EXPLORATIVE METHODS OF GASTRIC SECRETION IN STOMACH DISEASES (ULCER, CANCER, GASTRITIS, NEUROSIS WITH DIGESTIVE DISTURBANCES)

The gastric secretion was followed up by a personal special record card, before and after alcohol, insulin and histamine. The studied parameters were: the volume of gastric secretion per hour (V. H.), the maximal acid output per hour (M. A. O.), the buffer potency (B. P.), the deficiency in acid per hour (D. A. H.), the ration between the basal and stimulated secretion, the acid/alkaline secretion ratio, and in some cases investigations of the electrolytes of the gastric juice.

The conclusions of the authors are the following:

1. Each gastric tubing, in order to draw conclusions, has to be repeated, because there are situations when the stomach can temporarily lose the property to secrete its usual quantity of HCl. Its secretory function can for different reasons be diminished or abolished for a shorter or longer period. It is imperative to repeat the tubing, especially when achlorhydria is found.

2. In gastritis, gastric ulcer and gastric cancer, the greatest and most constant value of acidity appears after the use of histamine.

3. After alcohol there are variations from day to day, especially in neurosis with digestive disturbances and in duodenal ulcers. In patients with hyperalgesic forms of duodenal ulcer, there were higher values transfer after insulin than after histamine.

4. In some patients the V. H. transfer after histamine increased more than the ratio of HCl. The authors inquired whether this was due to hypersensitivity of the gastric mucosa to histamine.

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Abstract of presentation made during Congressus Gastroenterologiae Internationalis, VIII, in Prague, 1968.

CONDITION OF THE PANCREAS IN CIRRHOSIS OF THE LIVER

The function of the pancreas was examined in 181 patients suffering from cirrhosis of the liver. To evaluate the external pancreatic secretion, the activity of blood pancreatic enzymes (amylase and amylase curves, trypsin inhibitor and lipase) was studied, and intestinal absorption of fat and proteins was examined by means of radioactive isotopes. Morphological findings were considered in 18 cases (post-mortem examination).

Seventy patients displayed a disturbance of pancreatic function, those with portal and biliary cirrhosis in particular. Scanning of the pancreas (Z-Se-75-selenium-methionine) showed diminution of the absorbing capacity. A simultaneous lesion of the pancreas and intestinal wall was revealed in 18 patients with cirrhosis of the liver and ascites by means of the subsequent use of two radioactive substances (glycerin trioleate and oleic acid). Involvement of the intestine was confirmed by needle biopsy.

A close dependence was observed between the severity of the liver affection and the degree of abnormalities in the pancreatic function tests.

Fibrosis of the pancreatic tissue and the presence of atrophic and hypotrophic islets in it were encountered in cases with portal cirrhosis. In postnecrotic cirrhosis of the liver attended with hepatic coma, vascular disorders prevailed in the pancreas: congestive hyperaemia, stasis, and the presence of nonfibrinous thrombi. Destructive and necrotic foci were found in the hepatic and pancreatic tissue in the active phase of cirrhosis.

The possibilities of various diagnostic methods are discussed in the report.

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Abstract of presentation made during Congressus Gastroenterologiae Internationalis, VIII, in Prague, 1968.

PRIMARY SYPHILIS OF THE ANORECTAL REGION

Nowadays homosexual behaviour plays an important part in the transmission of syphilis; homosexual contacts seem to be responsible for about 25-50% of primary syphilis in males. The patient is likely to ascribe his anal symptoms to piles. Experience has also shown that the disease is unlikely to be correctly diagnosed in its primary stage. Because a venereal disease is seldom suspected in this area, the patients as a rule are not referred to a venereologist but to a surgeon interested in enterology. Ten cases of anorectal syphilis have been seen in our Department during the years 1958-1967. Excluding a female where the lesion looked like an early carcinoma of the rectum, the group consisted of nine single men, all admitting homosexual exposure. Anorectal syphilis has to be diagnosed early, as the local changes rapidly disappear and heal spontaneously within three to four weeks. Among the diseases to be considered in the differential diagnosis of this region are anal fissure, hemorrhoids and anal manifestations of Crohn's disease, basal and squamous cell carcinoma of the anal canal and even carcinoma of the rectum. It is probable that the comparative rarity of the cases is more a case of overlooking or misinterpreting the lesions, than a low frequency of luetic infections of the anorectal region. An improved awareness of the possibility of syphilis in this region will allow earlier diagnosis and treatment and prevent spreading of the disease.

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Abstract of presentation made during Congressus Gastroenterologiae Internationalis, VIII, in Prague, 1968.

CLINICAL AND HISTOLOGICAL FINDINGS OF ALCOHOLIC LIVER DAMAGE

The authors studied clinicopathologically 150 patients who had taken over 135 g of alcohol almost daily, and analyzed alcoholic hyaline with light and electronmicroscope according to Mallory's experimental report.

From the findings of biopsy examination, these cases were classified into several groups, such as hepatosis, hepatitis-type, fibrosis, precirrhotic type and cirrhosis. Variable necrosis was found in parenchyma and around portal fibrotic area; inflammatory cell infiltration in necrosis was ordinarily mild. In repeated biopsy examinations, liver cell changes were capable of returning to normal; however, necrotic changes turned to fibrosis and proceeded to pseudolobules, especially in patients who did not cease alcoholic ingestion.

We would like to emphasize necrotic process as a very important factor leading to pseudolobular formation.

Liver function tests, especially bromsulphthalein and ZST, were parallel to histological findings. The amount of alcohol ingested daily was somewhat correlated to the degree of histological findings; nutritious factor also seemed to contribute to the phenomena considerably. These alcoholics were mostly of low income.

Typical alcoholic hyaline was found in only two cases. Histological study of hyaline will be discussed according to Mallory's work.

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Abstract of presentation made during Congressus Gastroenterologiae Internationalis, VIII, in Prague, 1968.

NATURAL HISTORY OF RECTAL POLYP

In a seven-year study of 132 patients whose rectal polyps were left intact a total of 414 sigmoidoscopies were performed. The patients were examined periodically with both photography and cytologic examinations. The average age was 64 years. Of the 132 patients, 52 died without cancer of the colon or rectum. In five patients repeated follow-up examinations failed to detect the polyp. In 16 patients the original polypoid lesion showed malignant cytology and was removed because of suspected malignancy; these were true cancers. Two patients had suspicious cells on cytology and the polyp was removed through the proctoscope; on biopsy these polyps had only foci of malignant glands. In three patients the follow-up period was too short to be meaningful. Of the remaining 54 patients, four developed malignancy of the large bowel; these four were sigmoidoscoped on 23 occasions and had an average follow-up of 38.7 months, representing a total of 154 "polyp months." One of these cancers was a carcinoid and three appeared in areas other than the originally detected polyp. The remaining 50 patients had an average follow-up of 22.3 months, giving a total of 1,115 "polyp months." The appearance of benign rectal polyps did not change during the years of follow-up.

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Abstract of presentation made during Congressus Gastroenterologiae Internationalis, VIII, in Prague, 1968.

RESULTS OF MEDICAL THERAPY IN ULCERATIVE COLITIS

A review of a series of patients who were treated conservatively in the pre-steroid era revealed that complete symptomatic and proctoscopic remission took place in 7 percent in one month and reached 40 percent in six months. The remission rate in a group of patients recently treated with steroids was 13 percent in one month, reaching 47 percent in six months. The remission rate in a series of patients on sulfasalazine was similar to that observed with steroid therapy, ranging from 14 percent in one month to 40 percent in six months.

The relapse rate in patients who had achieved a remission without benefit of either steroids or sulfasalazine was 18 percent in one month, whereas the relapse rate after steroids was 37 percent in one month. At six months the incidence of relapse was 45 percent in symptomatically treated patients and 57 percent in the steroid group.

The effect of steroids in causing a more rapid remission in ulcerative colitis and the tendency to relapse when steroids are discontinued, are both in accord with the view that steroids act by inhibiting the inflammatory reaction in the bowel. Sulfasalazine also appears to act in a similar manner although somewhat more slowly.

A. Flood, M.D., J. Sweeting, M.D.*
New York, New York

*College of Physicians and Surgeons, Columbia University, New York.

Abstract of presentation made during Congressus Gastroenterologiae Internationalis, VIII, in Prague, 1968.

CLINICAL AND EPIDEMIOLOGICAL STUDIES ON CARCINOMA OF THE PANCREAS

Clinical observations of carcinoma of the pancreas were made in 1070 collected cases confirmed by histology, necropsy or laparotomy in Japan during the nine years from 1959 through 1967. In this series there were 703 males and 367 females. In 1030 of 1070 cases, symptomatology, histological classification, average survival period, surgical procedure, and prognosis were studied according to the site of lesion.

Secondly, previous dietary, smoking, drinking habits were surveyed in 475 cases of carcinoma of the pancreas among the collected cases, as well as hundreds of thousands healthy control-adults interviewed in 29 health center districts in Japan. The relative risk of carcinoma of the pancreas was calculated in both study and control groups. It was noted that the risk of this malignant disease was significantly higher in patients who were heavy smokers, had the habit of daily drinking alcoholic beverages, and also ate fewer green-yellow vegetables.

K. Ishii, M.D., T. Hirayama, M.D., K. Nakamura, M.D., H. Ozaki, M.D.*,
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Abstract of presentation made during Congressus Gastroenterologiae Internationalis, VIII, in Prague, 1968.

CLINICAL DIAGNOSIS OF CANCER OF BODY AND TAIL OF PANCREAS

On reviewing the clinical records of Memorial Hospital (New York City) from 1926 through 1965 there were 150 patients with histologically-proved carcinoma of the body or tail of the pancreas. The salvage from this neo-

plasm is low, largely due to the fact that the diagnosis is not made until the disease is far advanced. A review of the symptoms and findings in these 150 patients is presented to emphasize the difficulty of early diagnosis and, in so doing, to encourage the practitioner to suspect the diagnosis more frequently when confronted with a patient complaining of abdominal pain, bowel irregularities and insensible loss of weight.

L. Bowden, M.D., A. Die-Goyanes, M.D.*
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*Memorial-Sloan Kettering Institute, New York.

Abstract of presentation made during Congressus Gastroenterologiae Internationalis, VIII, in Prague, 1968.

EFFECT OF TREATMENT WITH THE ANTITUBERCULOUS DRUGS PYRAZINAMID AND ETHIONAMID ON THE LIVER

In 48 patients with pulmonary tuberculosis treated with pyrazinamid and/or ethionamid possible hepatotoxicity of these drugs was followed by means of a battery of liver tests and liver biopsies. In the majority of patients the liver tests and the histological examinations of the liver were performed both before commencement of treatment and after three to six months of treatment with the antituberculous drugs. Neither the liver tests nor the liver biopsies indicated any harmful effect of the treatment with pyrazinamid and ehionamid. Owing to a possible individual sensitivity regular examinations of the liver are still recommended during treatment with the antituberculous drugs.

O. Ostádal, M.D., M. Kubasta, M.D., V. Jezdinská, M.D.,
J. Dusek, M.D., J. Polásek, M.D.*
Moravia, Czechoslovakia

*Department of Pulmonary Diseases, IIIrd Department of Internal Medicine, Department of Pathology, Medical Faculty, Olomouc.

Abstract of presentation made during Congressus Gastroenterologiae Internationalis, VIII, in Prague, 1968.

GROWTH RETARDATION IN CHILDREN WITH INFLAMMATORY BOWEL DISEASE

Defining growth retardation as height below three standard deviations from normal, we have identified 25 children with growth retardation associated with inflammatory bowel disease. These 25, 16 male and nine female, represent 10% of the child population at the University of Chicago Hospitals. Fifteen (60%) had small intestinal disease (regional enteritis or ileocolitis) and 10 (40%) colonic disease (ulcerative colitis or granulomatous colitis). Nine had malabsorption. Though 23 patients received corticosteroids, there was retardation of growth in eight individuals (33%) prior to any form of therapy and in six (25%) preceding any gastrointestinal symptoms.

Two of four patients did not manifest a significant growth hormone elevation in response to insulin-induced hypoglycemia (assays on the remainder are in progress).

Other considerations include the vulnerable age range, extent and severity of disease, presence of other disorders (emotional, renal and hepatic) and the effectiveness of therapy directed to the intestinal disease (corticosteroids and intestinal resection) as well as to the growth problem (androgens).

K. Nasr, M.D., A. M. Lawrence, M.D., J. B. Kirsner, M.D.*
Chicago, Illinois

*Department of Medicine, University of Chicago.

Abstract of presentation made during Congressus Gastroenterologiae Internationalis, VIII, in Prague, 1968.

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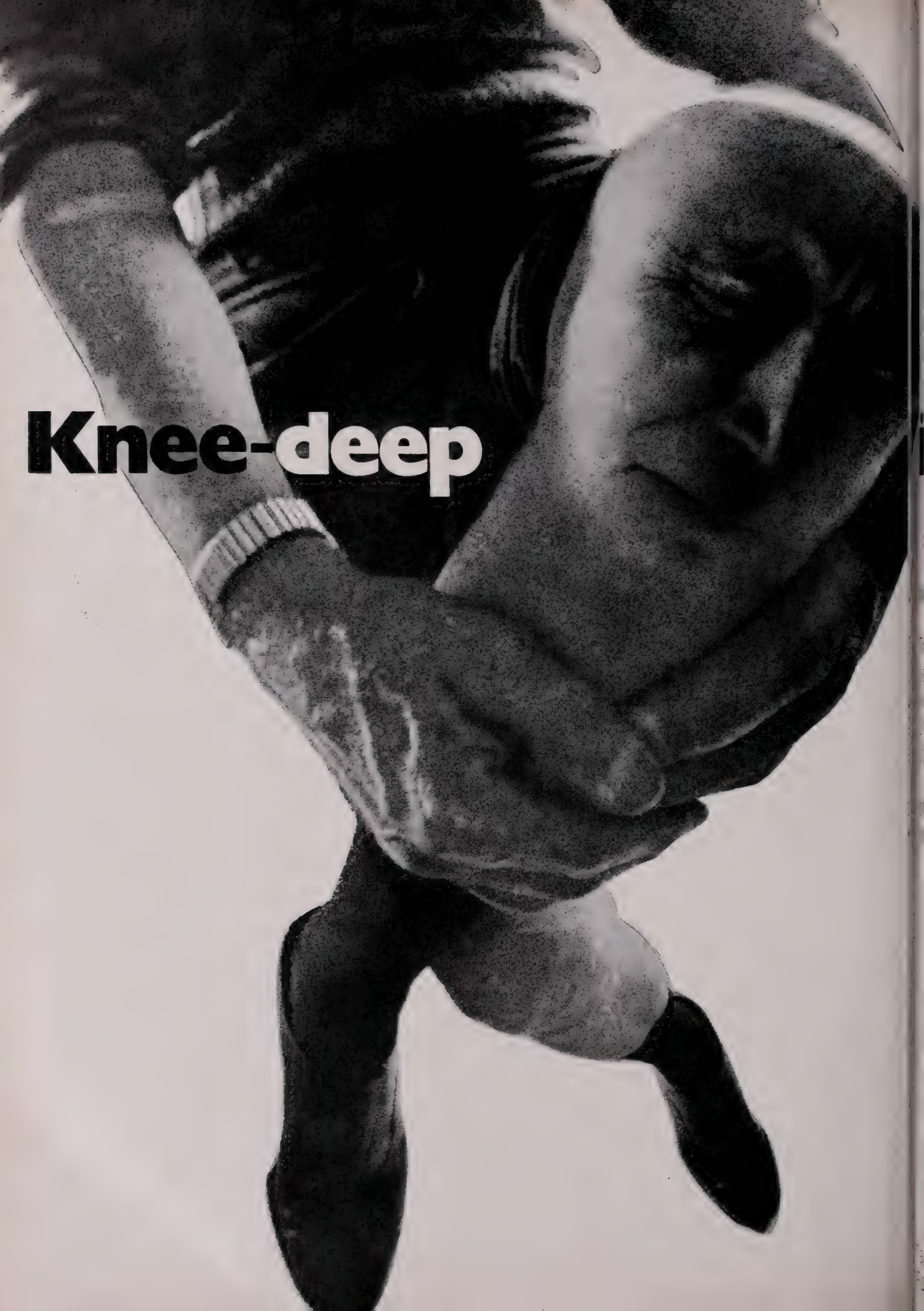
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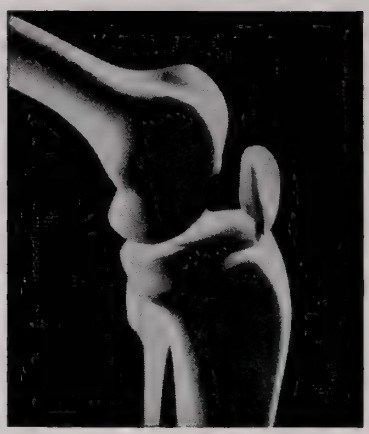
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For brief summary see next page.

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Warning: This drug is an analog of phenylbutazone; sensitive patients may be cross-reactive. If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Instances of severe bleeding have occurred. Persistent or severe dyspepsia may indicate peptic ulcer; perform upper gastrointestinal x-ray diagnostic tests if drug is continued. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy. Use with caution in the first trimester of pregnancy, and in patients with thyroid disease.

Precautions: Before prescribing, carefully select patients, avoiding those responsive to routine measures as well as contraindicated patients. Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patients should not exceed recommended dosage, should be closely supervised and should be warned to discontinue the drug and report immediately if fever, sore throat, or mouth lesions (symptoms of blood dyscrasia), sudden weight gain (water retention), skin reactions, black or tarry stools or other evidence of intestinal hemorrhage occur. Make complete blood counts at weekly intervals during early therapy and at 2-week intervals thereafter. Discontinue the drug immediately and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.

Adverse Reactions: The more common are nausea and edema. Swelling of the ankles or face may be minimized by withholding dietary salt, reduction in dosage or use of diuretics. In elderly patients and in those with hypertension, the drug should be discontinued with the appearance of edema. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. The patient should be instructed to take doses immediately after meals or with milk to minimize gastric upset. Drug rash occasionally occurs. If it does, promptly discontinue the drug. Agranulocytosis, exfoliative dermatitis, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), or a generalized allergic reaction similar to a serum sickness syndrome may occur and require permanent withdrawal of medication. Agranulocytosis can occur suddenly in spite of regular, repeated normal white counts. Stomatitis, salivary gland enlargement, vomiting, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported. While not definitely attributable to the drug, a causal relationship cannot be excluded. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, hypersensitivity angiitis, pericarditis and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.

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Organ Transplants

THE IDEA OF joining the organs of one animal to another is an ancient dream of man. The powers to accomplish such a feat were once attributed to supernatural beings, and from mythology come tales of mermaids, minotaurs, harpies, chimeras and many other strange combinations of man and beast that were both worshipped and feared. In fact, we turn to mythology for some of the vocabulary of transplantation biology. The chimera of Greek mythology, a she-monster with a lion's head, a goat's body and a serpent's tail, is the biologic term for a mixture of tissues of different genetic constitution in an organism.

The first recorded scientific investigation of tissue transplantation from one animal to another was made in 1771 by the English surgeon, John Hunter.[1] He wrote that he "took a sound tooth from a person's head, then made a pretty deep wound with a lancet into the thick part of a cock's comb and pressed the fang of the tooth into this wound, fastening it with threads passed through other parts of the comb."

Basic Concepts

The "modern era" of the transplantation story begins in 1903 with the discovery by Danish biologist, C. O. Jensen, that tumors which arose spontaneously in mice could sometimes be propagated by grafting them from one mouse to another.[2] He recognized that mice of different "races" were not all equally susceptible to the growth of the tumors he was studying. At about the same time, Carrell was developing the techniques of vascular suture which made renal transplantation technically possible. The first successful long-term renal autotransplant was performed in a dog by Zaaijer in 1908.[3]

By 1914 Carrell had begun to realize that homografts behave differently from autografts, but it remained for Ingebrigsten and Little to show that the failure of homografts to survive was due to biologic differences between donor and recipient.[2,3] From 1923 to 1926 there was a flurry of renal homo- and hetero-transplantation studies in animals with no identification of the basic immunologic problems involved.

Medawar's Research

Finally, however, in 1944, in work which was to win him the Nobel prize, P. B. Medawar demonstrated the immunologic basis for the homograft rejection.[4] Working with skin homografts in rabbits, he outlined six general features which are characteristic of the homograft reaction[5].

Latent Period

Homotransplants of skin undergo normal primary healing and vascularization during a latent period following transplantation; during this time they provoke no specific reaction from their hosts.

Intensity of Reaction Inversely Related to Tissue Dose

Between the fourth and the eighth days an acute inflammatory reaction begins with vascular and lymphatic proliferation, followed by invasion of the graft by monocytes and lymphocytes. The graft and its bed show marked edema. The regional lymph nodes draining the site hypertrophy and show infiltration by similar cells. Inflammation reaches its peak and passes on to necrosis, with the stagnation and obliteration of the vascular system of the graft and the death of its cellular

*This is a medical student activity, wholly conducted by students and our student editor.

elements. The entire process of breakdown is complete within a span of four days. Medawar[4] reported the median total survival time to be 10.4 plus or minus 1.1 days, but this varied inversely with the tissue dosage.

Sensitized State

If a second graft from the same donor is applied following rejection of the first, it is rejected much more rapidly, with rejection nearly complete by the fourth day following transplantation. This accelerated rejection of a second graft from the same donor is referred to as the second-set phenomenon and is regarded as evidence of the existence of a sensitized state in the host.

Sensitivity Extends Through the Body

McKhann and Berrian[6] found that three to four days of contact was necessary to produce immunity in mice using skin grafts, and that it was not affected by repeatedly breaking the continuity of contact between graft and host by turning the graft in its bed or by moving the graft repeatedly to new sites on the host during the necessary three to four days of contact. Thus the development of immunity was not contingent on establishment of vascular continuity or the sensitization of a single set of regional lymph nodes, but the sensitivity extended with equal force throughout the vascular territory of the body.

Sensitivity Directed Against Donor

It was Medawar who established that the homograft reaction was an immunologic reaction, thereby disproving Ehrlich's hypothesis that inevitable differences in the chemical constituents between individuals accounted for the death of transplants on a purely nutritional basis. In support of his theory Medawar[7] cited the existence of a phenomenon superficially akin to the immunologist's secondary response.

Sensitivity Does not Distinguish Between Different Tissues from Donor

This second-set phenomenon shows exact specificity and may be induced either by a graft or by injecting living cells from the donor. Further, there exists a phenomenon analogous to passive transfer of immunity. Mitchison[8] showed that lymphoid cells from the regional lymph nodes of a mouse which has reacted against a local solid tumor homograft have the power to confer sensitivity upon a normal mouse. This second mouse will respond to a homograft of the same type of tumor with a second-set reaction. Finally, reactivity against homografts can be prevented by taking advantage of immunologic tolerance.

Humoral vs. Cellular

Although it is now generally accepted that the homograft reaction represents an antibody-antigen type reaction, it is not yet fully understood what role humoral antibodies play compared to cellular mechanisms, for sensitivity to grafts can routinely be passively transferred by cells, not by serum; but the passive transfer of immunity can occur to skin grafts in rabbits[9] and mice[10] by enclosing sensitized lymphoid cells within diffusion chambers which prevent escape of the cells. On the other hand, if a graft is enclosed within a similar Millipore chamber which prevents ingress of cells but supposedly lets in smaller particles, the graft survives much longer than would be expected.

These observations raise several questions: Are the cells which are observed infiltrating a rejecting graft drawn there by a specific antibody-antigen complex, or is this a non-specific response? Are the cells acting as manufacturing plants for antibodies? If so, why does hyperimmune serum not convey immunity to another member of the same species?

Specific or Non-Specific

Lymphoid cells labeled with tritiated thymidine and sensitized to the homologous skin donor were passively transferred to homografted isologous hosts. This led to an accelerated rejection in 39 of 46 cases.[10] However, though 33% of the cells in the suspension were labeled, only occasional labeled cells were found among the infiltrate at the site of rejection. Yet a similar accelerated rejection could not be brought about by simply transferring serum from sensitized hosts. Thus the cells were necessary for the reaction, but they did not actually have to be present at the site of rejection.

Manufacturing Plant for Antibodies

Another experiment took advantage of the fact that in sheep and goats, xenografts* produce a rejection pattern that is similar both temporally and histologically to that observed with allografts in these species. Hyperimmune plasma was obtained from sheep and goats 16 days after reciprocal skin grafts and six days after reciprocal kidney transplants.[11,12] Three hundred milliliters of this hyperimmune serum was then transferred to each of 10 sheep and 10 goats that had received reciprocal kidney transplants. The result was an accelerated rejection. Furthermore, I^{125}-labeled gamma globulin from the hyperimmune plasma showed a seven-fold increase in localization in the transplanted kidney when compared to the remaining host kidney. Passive transfer of serum from non-sensitized hosts did not accelerate the reaction, nor did the same protocol produce an accelerated rejection of renal allografts. Why should immunity to xenografts be transferred by serum while immunity to allografts is not? A possible explanation lies in the fact that the organs of an animal probably share a number of antigens which are common to the species, not just the individual. Hence when dog A produces antibodies against the kidney of dog B, he also produces antibodies against a number of antigens that are shared by all dogs. When hyperimmune serum is passively transferred to dog C, the common dog antigens contained in dog C immediately complex the available antibodies and no transfer of immunity occurs. Such a situation is not encountered in grafting between different species.

Antibodies Released into Serum

A recent experiment reported by D. S. Clark sheds further light on the relationship between humoral and cellular mechanisms.[13] A kidney was transplanted from dog A to dog B and allowed to remain for 72 hours. The grafted kidney was then removed and 600 r of total body irradiation was given. This is a lethal dose and prevents further leukocyte replication. When the white count had dropped to 0-500 cell mm^3, a second kidney from dog A was transplanted to dog B and allowed to remain for two to 12 hours. Recall that at this time dog B had whatever circulating serum antibodies might have been manufactured during the presence of the first transplant, but it no longer had any functioning, circulating lymphoid cells. This second kidney was observed to swell, become darker in color, and show a moderately reduced blood flow, but it continued to put out a concentrated urine of over 600 milliosmoles/kg, and there was no evidence of any leukocyte reaction within the kidney on biopsy.

After two to 12 hours, this second kidney was removed from dog B and transferred back either to its original host, dog A, or to an indifferent host, dog C. In either case, a rapid rejection with a florid, host-formed element response was observed; in effect, dog A ended up rejecting one of its own kidneys! As a control, dog B received a second kidney from dog D. This kidney was then transferred back to dog D or to dog E. No effect was observed. A further observation in this experiment was that complement consumption in the rejecting graft in dog A became measureable between the second and the twelfth hours. Apparently the second kidney from dog A underwent an antibody-antigen reaction while in dog B. Upon transfer back to dog A, the antigen-antibody complexes in the kidney caused the local infiltration of host lymphoid cells; the presence of these complexes is further evidenced by the drop in complement levels. The fact that cells are necessary for the production of these antibodies (i.e., they are not pre-formed like the blood group iso-antibodies) is shown by the lack of any effect on the kidney from dog D, to which dog B was not sensitized while cells were present.

This series of experiments seem to indicate that cells are necessary for the production of antibody, which is then released to the serum. The cellular infiltrate observed with rejection is a non-specific one; specifically sensitized cells do not have to appear at the graft site as a part of the rejection process.

Subcellular Factors

With the development of cell fractionation techniques, efforts have been made to identify

*See Test Your Word Score Page 1583.

the subcellular fractions involved in homograft sensitivity. Lawrence extracted a "transfer factor" from umanh leukocytes which allowed transfer of homograft sensitivity as well as delayed hypersensitivity.[14] This is another striking departure from the requirement in animals for intact cells to transfer homograft immunity. Lawrence found this transfer factor to be stable to storage in the frozen state, to repeated freezing and thawing, to deoxyribonuclease and ribonuclease and to lysis by distilled water. Mannick reported that ribonucleic acid extracted from sensitized lymph node cells led to accelerated rejection of donor-type skin homografts when given to normal recipients.[15]

Graft Antigen

The nature of the graft antigen which brings about the rejection process has received far less attention than transplantation antibodies. Dempster has suggested that natural tranplantation antigens do not exist.[16] He attributes responsibility for rejection to processes within the homograft itself as a reaction against unknown factors in the host. Other investigators have found, however, that the ability of various tissues to sensitize to a subsequent skin graft seems to correlate with their content of iso-antigens detectable serologically.[17] Hume further suggests that there is a definite chromosomal locus that controls transplantation antigenicity, and that there is a dominant and a recessive type.[18] The majority of experiments suggest that histocompatibility antigens are associated with both the external cell membrane and with internal membranous components of various cell organelles; but work in this field has been hampered by the lack of knowledge of the distribution of cell surface membrane material in the various fractions of subcellular studies.[17]

Tolerance

In 1945, Owen noted that most cattle twins at birth are erythrocyte chimeras, with each possessing some of the other's red blood cells.[19] Medawar and his co-workers showed that such cattle twins would accept skin grafts from each other, regardless of differences in sex, while grafts from third parties brought about a typical homograft rejection reaction.[20]

Burnett and Fenner proposed a general theory of immune response which accounted for the phenomenon of tolerance.[21] They suggested that body cells possess some type of "self-marker" and that during embryonic or early postnatal life (the exact time varying with the species) the capacity to recognize this marker is developed. Thus an antigen presented to the body before this capacity for self recognition had developed would cause that antigen to be interpreted as self in later life in that no immune response would be made to it.

Medawar and his colleagues originally defined tolerance as "the outcome of an induced central failure of the mechanism of immunological response brought about by the exposure of animals to antigenic stimuli before the maturation of the facility of immunological response."[22] They showed that dead cells elicit neither tolerance nor tissue transplantation immunity. Shortly thereafter it was demonstrated that tolerant mice were chimeras so far as their lymphoid cell populations were concerned.[23] The experiments of Smith and Bridges suggested that the duration of the tolerant state depended upon the persistence of the antigen.[24] This led Medawar to redefine tolerance as: "If an animal is exposed to antigen before it has developed the capacity to react against it, then the development of that capacity is delayed and, in the continued presence of that antigen, can be indefinitely postponed."[25] In his Nobel lecture, Medawar outlined the following three properties of the tolerant state:[26]

1. Tolerance is due to an alteration of the host, not to an antigenic adaptation of grafted cells.
2. The state of tolerance is systemic; a graft from a tolerated genotype will survive at any location on the body.
3. The state of tolerance is specific in distinguishing one individual from another, but not in telling one tissue from another; if skin is tolerated, so is any other tissue.

A tolerated graft retains its power to provoke immunity when transplanted to a normal environment, but tolerance may be abolished by inoculating a tolerant animal with immunologically active cells.

Graft Versus Host Reaction

In 1957 Billingham and Brent found that in certain strain combinations, attempts to produce tolerance in newborn mice produced a peculiar wasting disease and eventual death.[27,28] They concluded that this condition was the result of a reaction of the graft versus the host (GVH), and named the condition "runt disease." Graft vs. host reactions result when the recipient of a graft of immunologically competent cells is incapable of rejecting the graft. For example, in grafting from a homozygous donor (AA) to the F_1 hybrid between the donor and a dissimilar homozygote (BB), a situation results in which the host (AB) is incapable of rejecting the graft because the graft possesses no antigens foreign to the host. However, the host possesses antigens foreign to the graft, producing a graft vs. host reaction if the graft consists of immunologically competent cells. Such a reaction can be prevented by: (1) injecting isogenic adult splenic cells shortly before foreign cells are injected; (2) injecting adult cells preimmunized against the donor; or (3) passive transfer of serum-containing antibodies to the antigens present in donor cells.[29]

Graft Alterations

There is some evidence that extended survival of homografts may, at least in some cases, be due to an adaptive change in the graft rather than in the host. Woodruff and Simpson noted in rats that skin homografts on animals rendered highly but not completely tolerant could continue to survive with no change in the gross appearance, whereas a second graft from the same donor was completely destroyed.[30] If the long-tolerated skin graft is transferred to a normal recipient, it is regularly rejected. Billingham suggests that the mechanism for the decreased vulnerability of long-tolerated grafts may be due, at least in part, to complete replacement of the vascular endothelium of the graft by endothelium of host origin.[22] However, this does not adequately explain the rejection of the graft when it is transferred to another member of the same species.

Clinical Application and Problems

By far the greatest clinical experience and success in organ transplantation has been with kidneys, though recent advances have also been made in transplantation of the liver and the pancreas. Between 1936 and 1951 there were several unsuccessful attempts at renal homotransplantation in man, using cadaver kidneys. In 1953 the first transplant was done by Michon and Hamburger in France,[3] using a kidney from a living donor. By July 1967, at the latest report of the kidney transplant registry, there had been 1178 kidney transplants. Transplants have been attempted in newborn infants (two, both unsuccessful) and in individuals past 50.

Indications and Contraindications

Long-term transplants have been carried out in patients whose renal failure was secondary to pyelonephritis, glomerulonephritis, Goodpasture's syndrome, essential hypertension, malignant hypertension, polycystic renal disease, congenital hypoplasia, cortical necrosis, traumatic injury, bilateral benign renal tumors with massive hemorrhage, renal carcinoma, Kimmelstiel-Wilson's disease, Alport's syndrome, and horseshoe kidney.[3] Transplants in patients over 50 years of age have met with a high rate of mortality; therefore 50 is now regarded as an upper age limit for transplantation. Transplants are contraindicated in patients with uncontrollable generalized infections, irreversible brain damage, or a generalized nonrenal systemic disease likely to be fatal.[3]

Just as selection of recipients requires careful screening and selection, so donor selection must be done with great care. It is possible to transmit cancer, infectious hepatitis, histoplasmosis, thrombocytopenic purpura and delayed hypersensitivities through kidney transplants.[3] Evaluation of the potential living donor must be directed toward an assessment of general health, renal function and motivation to donate.

Histocompatibility

Obviously it is desirable to have the donor as compatible as possible antigenically with the recipient, and a number of different tests for

determining histocompatibility between donor and recipient are currently under investigation. It has been found that erythrocytes contain little if any transplant antigen. Failure of a transplanted kidney in the face of ABO incompatibility is probably due to the representation of ABO blood groups within the vasculature of the kidney, with subsequent thrombosis of the vessels due to attachment of blood group antibodies.[3,31] Hence proper matching of blood groups is important, but not directly because of the transplant reaction.

Skin Graft Test

Hume describes five general types of histocompatibility tests.[3] The simplest test is merely to transfer a skin graft from the intended donor to the recipient. This method suffers from several drawbacks, however. There is risk of immunizing the intended recipient against the intended donor. Furthermore, there is not an absolutely predictable relationship between the rejection of a skin graft and the rejection of a kidney.

The Third Man Test

A skin graft from the intended recipient is placed on a volunteer, who forms antibodies against the graft as it is rejected. Then skin grafts from several possible donors are placed on the volunteer and the donor is selected whose skin is rejected most rapidly, on the theory that he has shared antigens with the intended recipient, causing the accelerated rejection in the immunized volunteer. While the test demonstrates similarities between the intended recipient and donor, it does not indicate differences between them; furthermore, the test is subject to the reactions of the volunteer against each of the donors on the basis of his own incompatability with them.

Normal Lymphocyte Transfer Test

In this test blood lymphocytes from the intended recipient are transferred intradermally to the intended donor, and the size of the erythematous wheal is measured. The test is difficult to quantitate accurately and has not been shown conclusively to be related to ultimate graft survival.

Mixed Lymphocyte Reaction Test

When lymphocytes are incubated in tissue culture medium, some of the small lymphocytes become transformed into large immature cells which synthesize deoxyribonucleic acid, as demonstrated by the uptake of tritiated thymidine. If cells from a potential donor and recipient are placed together in a tissue culture medium there will be an increased transformation of small lymphocytes into large forms, and the degree of increase is related to the degree of antigenic dissimilarity between the donor and recipient. The difficulty with this test is that it is impossible to tell whether the donor is reacting against the host or vice versa.

Leucocyte and Platelet Typing

Leucocyte agglutination and cytotoxicity of various sera as end points can be used, but there are still deficiencies in the ability of these tests to separate donor-recipient pairs who appear to be compatible clinically from those who do not.

Requirements for a Useful Histocompatibility Test

The test should:[32]

(1) Be able to exclude any donor whose organs would elicit a particularly violent response in the recipient.
(2) Be able to pick out individuals from a group of possible donors whose tissue would be tolerated for the greatest possible time.
(3) Not lead to sensitization of a future recipient.
(4) Be quick to execute and have a high degree of discrimination.
(5) Be capable of use on debilitated or uremic patients.
(6) Be applicable to cadaver donors.

Currently only requirement number three can be met. Furthermore, the choice of living donors for any particular recipient is usually so limited that one does not have the luxury of choosing the most compatible donor.

Pathophysiology of Rejection

Clinically

The classic signs of threatened rejection

are fever, swelling and tenderness of the transplant and operative site, mild anorexia, and a fall in urinary output.[3,33] The laboratory provides further clues, including the appearance of lymphocytes in the urine, a change in serum lactic dehydrogenase, an increase in kidney size on X ray, a fall in the level of the second component of complement, a change in blood urea nitrogen and serum and urinary creatinine levels, and an increase in urinary alkaline phosphatase and lysozyme activity, as well as a fall in clearance for hippuran, Co^{57}, vitamin B_{12}, inulin, and creatinine.[33]

Microscopically

The tissues will show interstitial edema and infiltration with small lymphocytes, plasma cells, round cells, and pyroninophilic cells.[3,34,35,36,37] In the kidneys there is tubular damage with vascular necrosis and ischemia. Acute glomerular lesions, whether microscopic or ultrastructural, are rare.[3,34,35,38] The later rejection is seen in the course of the transplant, the more prominent the vascular lesions become. Beginning at 24 to 72 hours there is swelling of the endothelial cells of arterioles and the interlobular arteries, followed by general intimal thickening, medial atrophy and fragmentation of the internal elastic lamina of all vessels. Muscular hyperplasia of the small arteries and hyalinization of the arterioles become more prominent with time. Ultrastructurally, the glomeruli and distal tubules are normal.[37] There is an increase in the number of cytoplasmic vacuoles as well as cytoplasmic shedding in the proximal convoluted tubules in canine studies.[39] However, there is not generally a good correlation of changes in function with microscopic changes.[3]

Control of Rejection

It is imperative that these rejection episodes be controlled, and most of the clinical attempts at modifying the homograft response have centered about the use of irradiation and chemotherapeutics.

Radiation

Local radiation of the graft has proven particularly useful with transplants from unrelated donors as indicated by the one-year survival for kidney transplants from unrelated donors which showed 21% for those without local radiation versus 33% when radiation is used; the figures for two-year survival are 15% without radiation and 28% with radiation.[40] Radiation has not been shown to bring about a statistically significant improvement in survival where related donors were involved.

Chemotherapeutics

These may be divided into several classes: steroids, antimetabolites, alkylating agents, and antibiotics. Considerable species variation has been noted in the response to chemotherapeutic agents.[41] Steroids do little to modify homograft rejection in dogs, but in high doses they may abort the rejection of human renal homografts. Six-mercaptopurine (6-MP) was one of the earliest antimetabolites to show marked prolongation of skin and renal homografts; however, toxicity of the drug rendered management difficult. Azathioprine (Imuran) was found to cause less bone marrow depression while retaining the effectiveness of six-mercaptopurine. Imuran has been shown to significantly augment survival of human renal transplants and is now used almost universally in the management of transplant cases.[42] In general, the alkylating agents (mustards and ethylene amines) have been less effective than antimetabolites in direct suppression of the homograft response. The demonstration that certain antibiotics interfere with protein synthesis led to their trial in attempts to suppress the immune response. Most of the studies on suppression of the homograft reaction have utilized actinomycin C, which led to prolonged survival of renal transplants in dogs and man when used in conjunction with Imuran.

Complications of Drug Therapy

Physiologic

The use of chemotherapeutic drugs has led to a host of new problems. Gastrointestinal bleeding, secondary infections, diabetes, and cataracts have been not infrequent problems with steroid therapy. In studying 26 post-transplant patients ranging in age from 11 to 50 years, Hovland found that eight developed increased ocular pressures ranging

from 22 to 38 mm. Hg.[43] Twelve developed posterior subcapsular lens opacities. No significant correlation existed between the dose of prednisone and Imuran and the development of the lens opacities, however.

Infections

In a study of patients who died while receiving immunosuppressive therapy for organ transplantation, pulmonary infections were found to be present in 26 of 32.[44] Multiple infections were common, and the organisms found were not those usually responsible for clinical diseases; they included Candida, Aspergillus, Nocardia, Pneumocystis and Cytomegalovirus.

Imuran has been associated with pancreatitis, liver toxicity, and marrow hypoplasia. Thus in the case of liver transplants we have the unique situation of using a drug that is toxic to the liver to help promote liver function.

Transplant Lung[3]

This syndrome involves an alveolar-capillary block with low arterial pO_2 and O_2 saturation and normal arterial pCO_2. Physical findings in the lung are absent or minimal. The chest X ray may look like miliary tuberculosis, pneumonia or splotchy pneumonitis; or it may be normal. These changes are sometimes accompanied by threatened rejection of the kidney transplant. Histologically there is pulmonary capillary damage, edema, and round cell infiltration of the alveolar wall.

Present Morbidity

Despite the many problems which still exist, progress is being made in the field of organ transplantation. The latest data from the kidney transplant registry shows that where related, living donors were used there has been a one-year survival of 55% and a two-year survival of 48%.[40] The figures for unrelated donors were cited earlier. If one considers only the experience since January 1, 1965, the one-year survival rates for related donors is 65%, and that with cadaver donors 39%. Furthermore, many patients who had crippling neuropathy or nerve paralysis prior to transplantation have no significant difficulty with these problems just six months after transplantation.[46] Patients who have been nearly blind from hypertensive retinopathy have vision again. The anemia of renal failure disappears.

Conclusion

The transplantation of tissues and organs as a practical and safe method of dealing with disease still awaits further progress in many areas. Advances are being made in the storage and preservation of tissue. The identification of the major specific histocompatibility antigens of an organ remains an unsolved problem of profound importance. When this is solved, techniques of cross-matching will be required. Finally, the complex immunologic processes that are activated by the presence of foreign tissue within the body are not fully understood; when these processes are finally identified, there will be profound imp'ications not only for the area of transplantation, but for cancer research as well.

As the problems which currently complicate transplantation are solved, however, the ethical questions surrounding the transplantation of human tissue will loom ever greater. Nolan has pointed out that there are problems with regard to both the recipient and the donor.[47] For the present, one must realize that transplantation is a method of treatment which is still at the experimental stage and still of debatable value. One must further consider that in doing a transplant, one is submitting a patient to a treatment which includes the pain and inconvenience of major surgery and other unpleasant procedures, when the chances of restoring him to life may be relatively small. Finally there looms the question of who should be transplanted and who should be maintained on chronic dialysis.

With regard to the donor, one must ask when one is justified in subjecting a healthy person to the risks of surgery? When can one make the diagnosis of death and allow a cadaver kidney to be removed? In making such a decision one must be careful not to allow the need for the kidney to influence one's care of a potential donor. The answers to these questions extend far beyond the medical research laboratory.

Robert R. Reick, M.D.*
Minneapolis, Minnesota

*From the James E. Moore Society (See Minnesota Med 51:1469, 196



Meetings and Announcements

A wise man knows everything; a shrewd one, everybody.—Anonymous

NOVEMBER

Southwestern Minnesota Medical Society, Worthington, 7:00 p.m., November 4.

Scott-Carver County Medical Society, County Society Meeting, 6:30 p.m., November 5, Wagner's Supper Club, Jordan.

Zumbro Valley Medical Society, Regular Meeting, Plummer Hall, 7:00 p.m., November 6.

Minnesota Academy of Ophthalmology & Otolaryngology, Minneapolis Club, 6:00 p.m., November 8.

Minnesota Society of Clinical Pathologists, Annual Tumor Seminar, Minnesota Club of St. Paul, November 9.

Camp Release District Medical Society, Hunt Hotel, Montevideo, 7:30 p.m., November 14.

St. Louis County Medical Society, Executive Meeting, 6:00 p.m., St. Luke's Hospital, Regular Meeting at 8:00 p.m., November 14.

Twin City Urological Society, Town & Country Club, 6:00 p.m., November 15.

Steele County Medical Society, Regular Meeting, Inn Towne Motel, 6:30 p.m., November 19.

West Central Minnesota Medical Society, Annual Election, 7:30 p.m., November 19 or 26, Pomme de Terre Country Club, Morris.

Blue Earth Valley Medical Society, Interlaken Golf Club, Fairmont, 7:00 p.m., November 20.

Kandiyohi-Swift-Meeker County Medical Society, Westwood Inn, Spicer, 7:00 p.m., November 21.

McLeod County Medical Society, Velvet Coach, Hutchinson, 6:30 p.m., November 21.

Blue Earth County Medical Society, Century Club, 6:00 p.m., November 25.

Ramsey County Medical Society, Clinical Meeting, St. Paul-Ramsey Hospital, 8:00 p.m., November 25.

Waseca County Medical Society, Regular Meeting, November 25.

Range Medical Society, Executive Committee, 6:00 p.m., November 26, General Meeting & Dinner, 7:15 p.m., place to be announced.

Clay-Becker County Medical Society, Meeting for election of officers, date and place to be announced.

Minnesota Thoracic Society, Mayo Clinic, 1:00 p.m., date to be decided.

DECEMBER

Nicollet-LeSueur County Medical Society, Christmas auction for AMA-ERF Fund, 6:30 p.m., December 2, Dinner, Holiday House, St. Peter.

Southwestern Minnesota Medical Society, Worthington, 7:00 p.m., December 2.

Minnesota Obstetric & Gynecological Society, Sheraton-Ritz Hotel, Minneapolis, 9:00 p.m., December 7.

Camp Release District Medical Society, Hunt Hotel, Montevideo, 7:30 p.m., December 12.

St. Louis County Medical Society, St. Mary's Hospital, Executive Meeting at 6:00 p.m., December 12.

Minnesota Academy of Ophthalmology & Otolaryngology, University of Minnesota, 9:00 p.m., December 13.

St. Louis County Medical Society, Annual Banquet, Kitchi-Gammi Club, 7:30 p.m., December 14.

Renville-Redwood County Medical Society, Redwood Falls Golf Club, 7:00 p.m., December 17.

Freeborn County Medical Society, Annual Meeting & Election of Officers, Dinner, December 19, 6:30 p.m., Albert Lea.

Kandiyohi-Swift-Meeker County Medical Society, Westwood Inn, Spicer, 7:00 p.m., December 19.

Blue Earth County Medical Society, To be announced at November Meeting.

Scott-Carver County Medical Society, Ladies Auxiliary Dinner Dance, time and place to be announced.

Waseca County Medical Society, Regular Meeting, December 30.

A Program of Clinical Experience in Outpatient Education for Control of Diabetes Mellitus

The Diabetes Detection and Education Center, 916 East 15th Street, Minneapolis, Minnesota, has developed a program of medical and paramedical education for physicians, nurses, public health personnel, and dietitians. Classes are scheduled for the weeks of: November 4, November 18, December 2, December 16, and December 30. Rooms and meals are available at the Center at minimum cost.

For further information, contact D. D. Etzwiler, M.D., or C. B. Cohen, M.D., 916 East 15th Street, Minneapolis.

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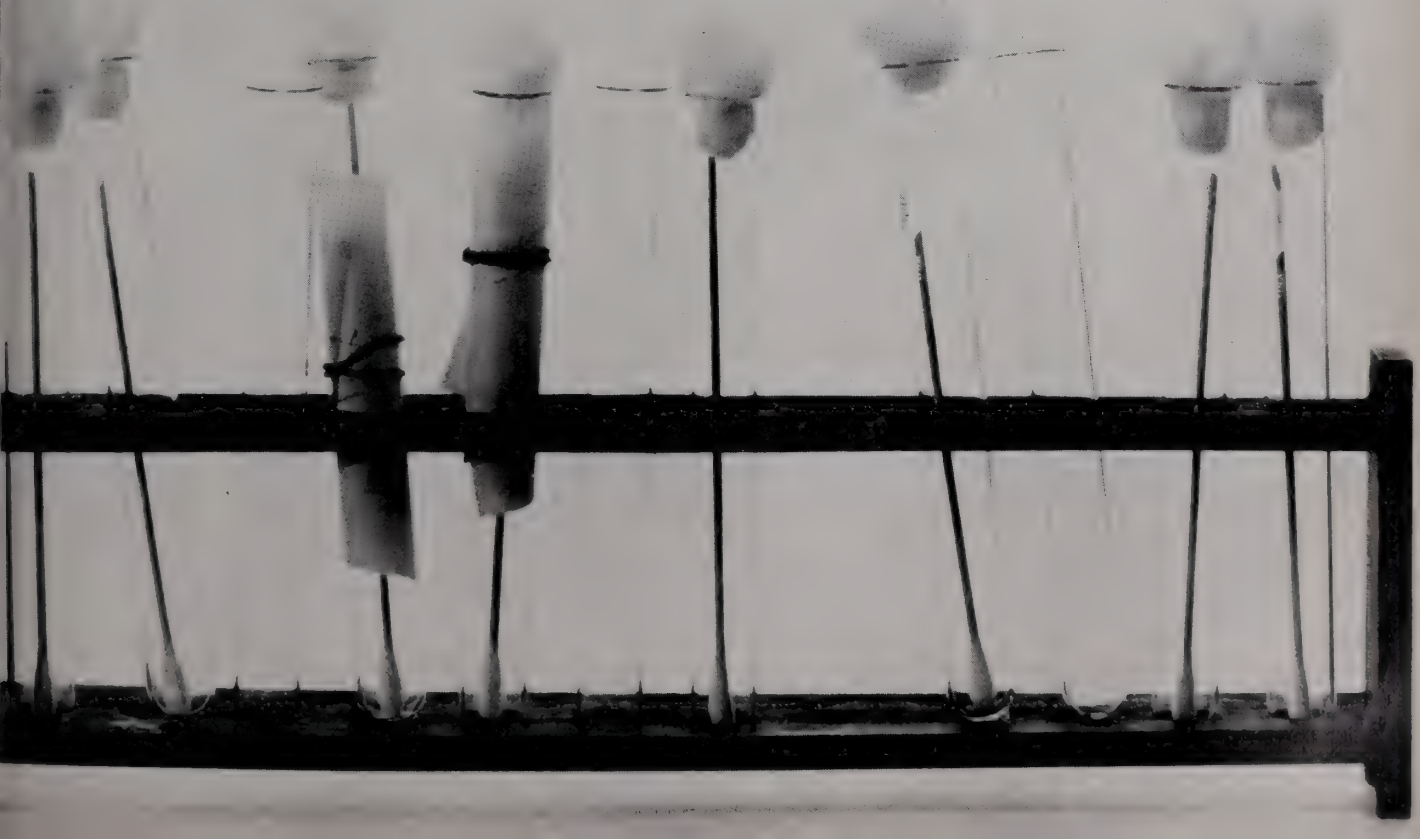
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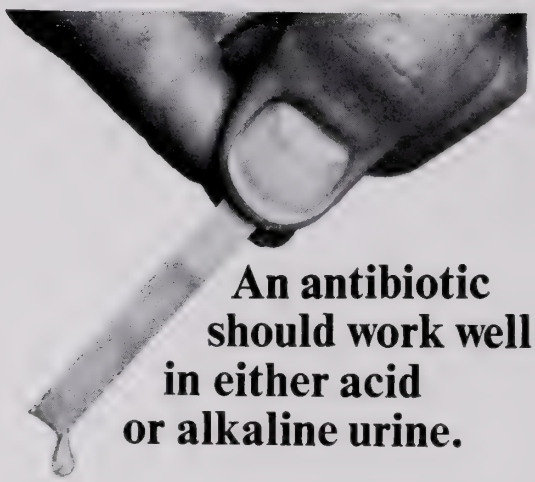
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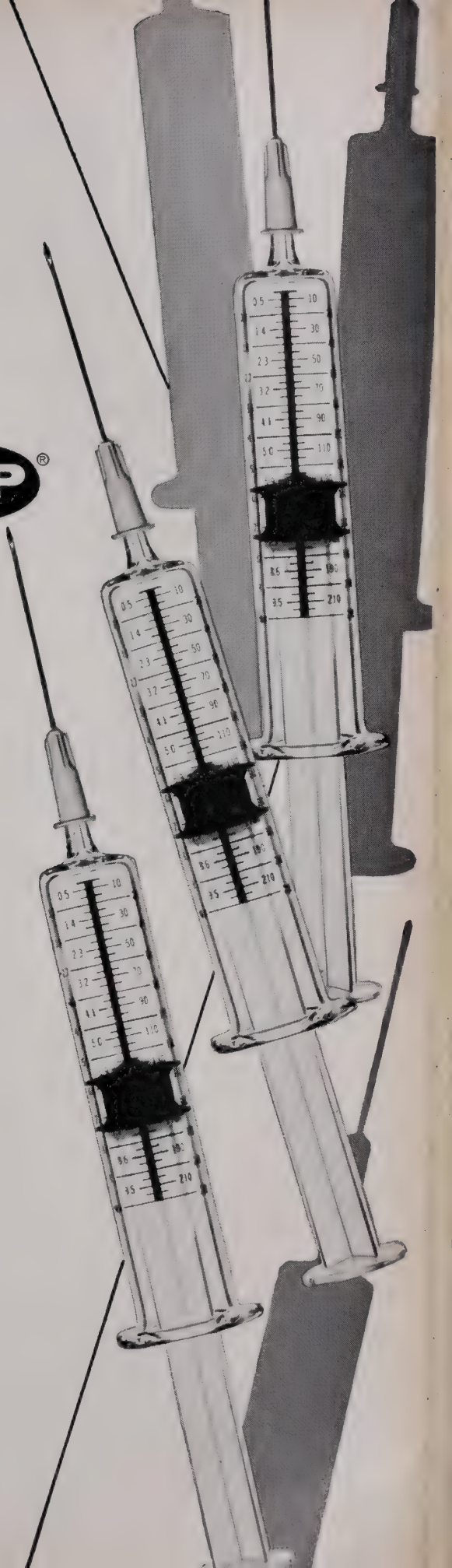
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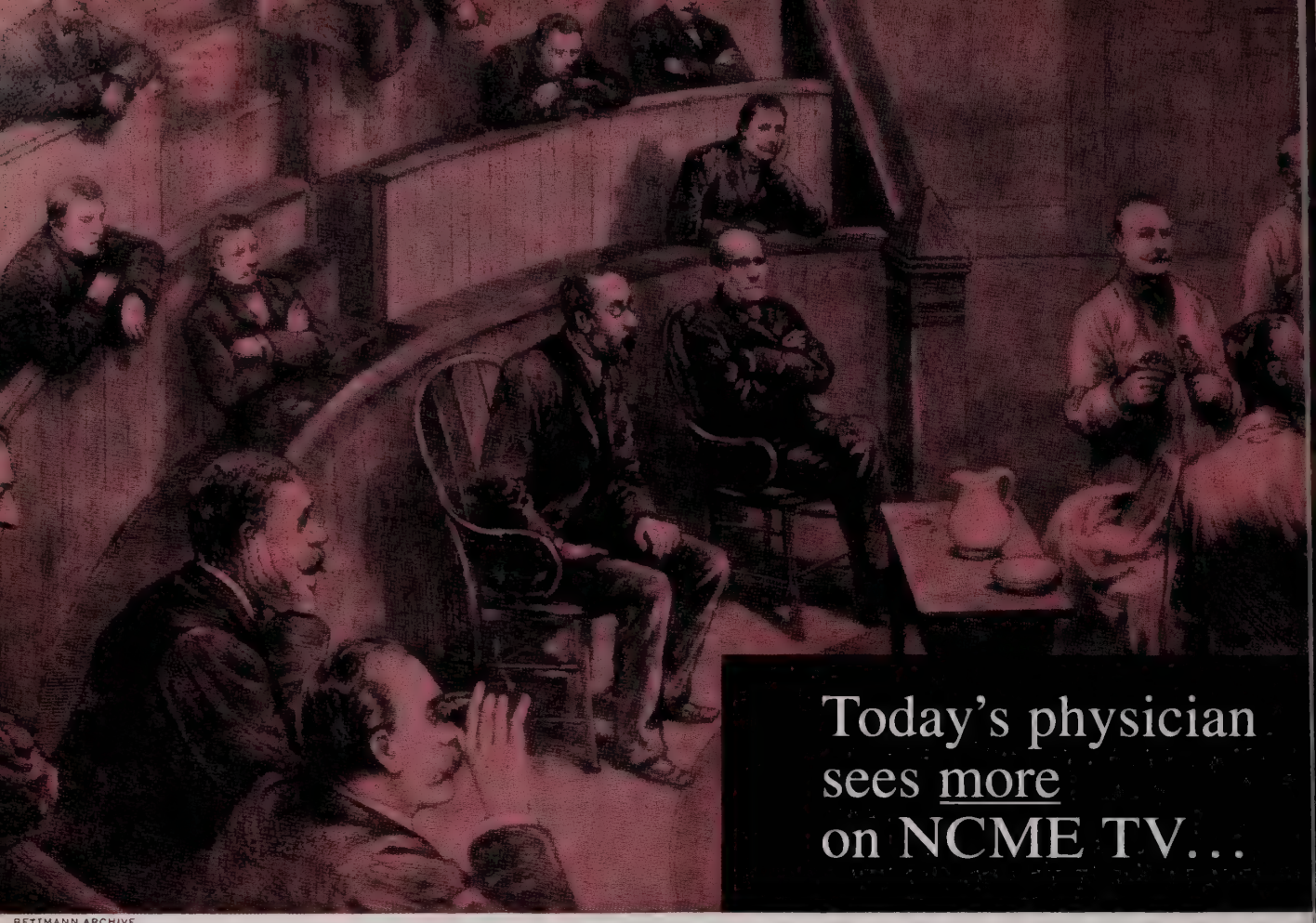
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Presidents' Letter



George A. Sather, M.D.



O. L. Norman Nelson, M.D.

As the curtain is about to be lowered on a fast-expiring 1968, it is time to declare a brief moratorium on Medicine's problems and frustrations. The holiday fortnight affords an opportunity for recovery, or at least convalescence, from the wounds of Medicare, Medicaid, comprehensive health planning, utilization review, expansion of the medical school, a new medical school, et cetera; and a new legislative session lies just ahead.

On behalf of the Council and the officers of your Minnesota State Medical Association, we bring you greetings. May yours be a traditionally Merry Christmas and a Happy New Year.

George A. Sather, M.D.
Chairman of Council

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STATE MEDICAL ASSOCIATION

minnesota medicine

Volume 51

Number 12

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1700 Vaginal Hysterectomies

In A General Surgical Practice

LESLIE W. TASCHE, M.D.
Sheboygan, Wisconsin

MANY GYNECOLOGICAL procedures still seem to fall within the domain of the general surgeon in a community such as ours (45,000). One of the more difficult gynecological problems encountered is that of prolapse of the uterus. The Watkins interposition operation, the combined procedure of anterior and posterior colporrhaphy* and abdominal suspension of the uterus, and the Manchester-Fothergill were methods used to correct this condition, but were often failures.

Material

This report is based on 1700 consecutive vaginal hysterectomies performed between January 1943, and May 2, 1968. During this same period of time, 707 abdominal hysterectomies were done. All of these women were Caucasian and were private patients. The average age was 52.7 years. There were 16 women under 31 years of age and 16 over 80, the oldest being 91. The greatest number were between the ages of 40 and 60.

Indications

The three types of disability most commonly encountered, probably covering 90% of the cases, were varying degrees of prolapse, bleeding, and stress incontinence. Fibroids and cervical disease constituted most of the remaining 10%. Seldom was one of these conditions present alone. Gray[1] summarizes these multiple lesions to include benign cervicitis, stenosis of the cervical canal after cauterization or conization, enlargement of the uterus, retroversion, vaginal discharge, dysmenorrhea, dyspareunia, menorrhagia, metrorrhagia,* low backache, pressure pain and bearing-down sensations.

Classification of Prolapse

Prolapse was classified into three stages: the first degree was considered present when the cervix could be pulled down an appreciable

*See Test Your Word Score Page 1757.

distance from its normal position, the second degree when it could easily be pulled down to the outside, and the third degree when it protruded outside of the vulva or beyond without any pulling

Major Symptom Complexes

Prolapse and Bleeding

The two major symptom complexes, prolapse and abnormal bleeding, were divided into two age groups (Table 1).

It can be seen (Table 1) that abnormal bleeding brings more patients to their physicians in the early age group and prolapse in the older.

The cause of bleeding in the 555 cases could only be surmised by checking against the most prominent pathological findings (Table 2).

Urinary Symptoms

Stress incontinence, frequency and the inability to empty the bladder were present in 359 women. Those women with first and second degree prolapse had just as many troubles with their bladders as those with greater prolapse (Table 3). Why this should be is difficult to explain.

Carcinoma of the Cervix

If carcinoma of the cervix was strongly suspected by Pap test or previous biopsy and the lesion was thought to be in situ or early first stage, vaginal hysterectomy was done, removing a wide cuff of vagina.

Endometrial Carcinoma

If endometrial carcinoma was suspected from either the patient's history or a positive Pap test, and if the uterus was freely movable and not enlarged, with relaxation of the perineum, and if the patient was aged or obese or a poor risk, a vaginal hysterectomy was performed without curettement. Routine prehysterectomy curettage was not done; but if suspicion of carcinoma was entertained, curettage or biopsy was first performed. If cancer was found, the vaginal hysterectomy was postponed until a report on the tissue was obtained. Curettings and biopsies have been difficult to diagnose by our pathologists on frozen section. It was also felt that a so-called gentle curettement may well disseminate the cells of even a small malignancy.

Procedure

At first, a modification of the Mayo type of vaginal hysterectomy was performed but, because of the relative frequency of the development postoperatively of an enterocele or rectocele, or both, this was discontinued and the methods and principles established by Heaney[2] and Waters[3] were followed. Practically all of the 1700 operations were performed under intravenous induction of sodium pentothal followed by inhalation anesthesia.

Preoperative Preparation

There was no special vaginal preoperative preparation except for a thorough soap-and-water scrubbing followed by the application of tincture of merthiolate. The bladder was catheterized until empty and the labia were sutured to the adjacent skin. A second preparation of the vagina with tincture of merthiolate was then made. The cervix was pulled down with one or two Vulsellum forceps.

TABLE 1

Prolapse					
20 to 49 yrs.			50 to 90 yrs.		
1°	2°	3°	1°	2°	3°
18	241	126	22	297	411

Abnormal Bleeding	
20 to 49 yrs.	50 to 90 yrs.
377	178

TABLE 2
Abnormal Bleeding

	Ages 20 to 49	Ages 50 to 90
Fibroids	127	56
Path. endometrium	153	44
Carcinoma	4	25
Polyps	35	33
No pathology	58	20

TABLE 3
Urinary Symptoms

	Ages 20 to 49		Ages 50 to 90	
	Total Cases	With Symptoms	Total Cases	With Symptoms
1st degree prolapse	18	8	22	9
2nd degree prolapse	241	96	297	101
3rd degree prolapse	126	27	411	118

Entering the Posterior Cul-de-Sac

The bladder was freed from the cervix upwards and the peritoneal cavity was entered anteriorly. If this was at all difficult, this step was postponed until the peritoneal reflection could be visualized through the posterior peritoneal incision (Figure 1).

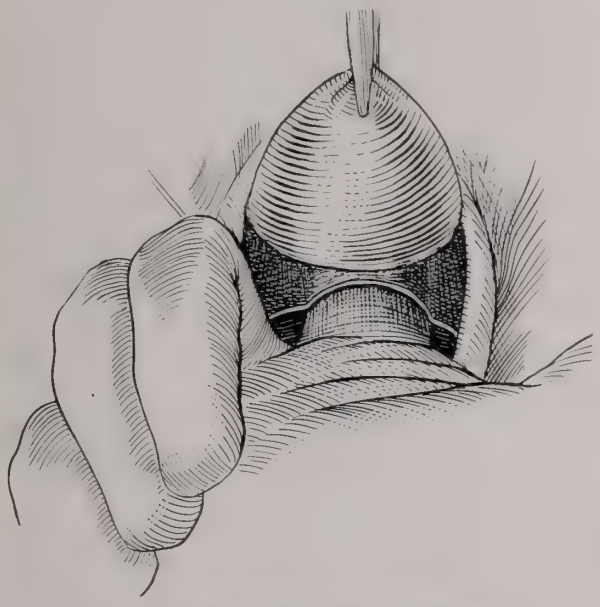


Fig. 1—Entering the posterior cul-de-sac.

Isolating the Ligaments

With the left index finger behind the lower cervical ligaments, a Heaney clamp was applied on the patient's left uterosacral and lower cardinal ligaments (Mackenrodt's) and the tissues divided (Figure 2).

Suturing and Dividing the Ligaments

A figure of eight double suture of chromic #2.0 was securely tied with the ends left long and clamped. The uterus on the patient's left side was then further freed by advancing the clamps upward and dividing and ligating each in turn, leaving the ends long and clamped (Figure 3). This was done until the tubes and the round and utero-ovarian ligaments were reached. It is very important that the bladder, ureter, and other tissues be pushed to one side with a retractor while this is being done. The procedure was then continued in the same manner on the other side (Figure 4).

Delivery of the Uterus

The ovarian ligaments and tubes were finally clamped on each side after bringing the uterus outside either anteriorly or posteriorly (Figure 5), whichever seemed the easiest. A weighted speculum was then placed in the vagina with the tagged ligatures lying on each side. The ovaries were examined; if any pathology existed it was removed.

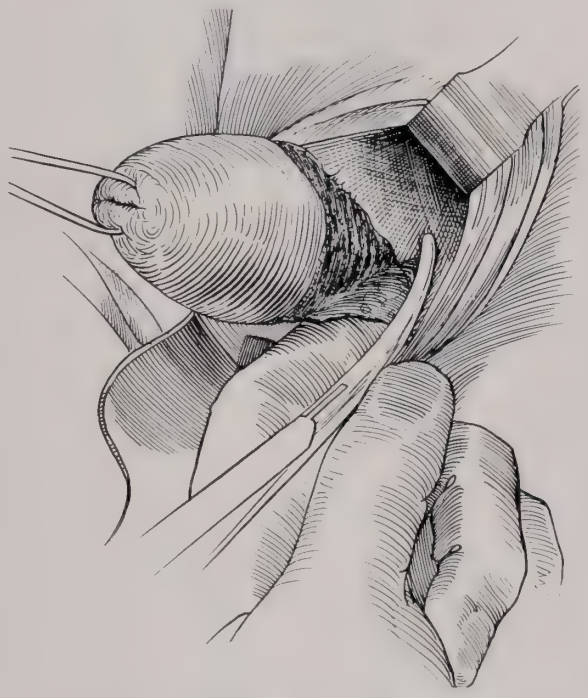


Fig. 2—Isolating and dividing the ligament.

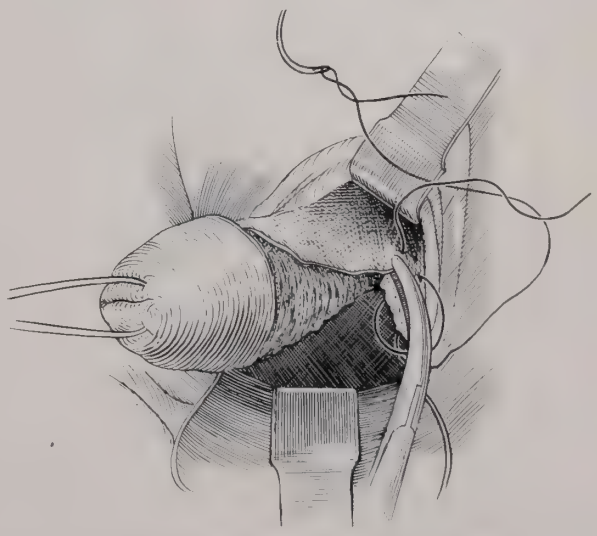


Fig. 3—Suturing of the ligament on left.

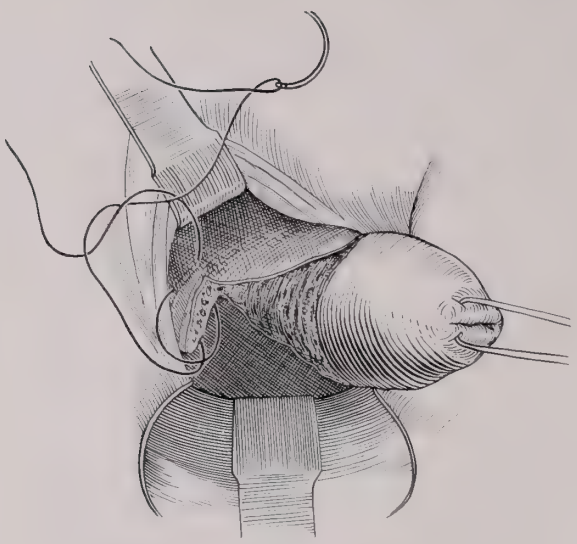


Fig. 4—Suturing of the ligament on right.

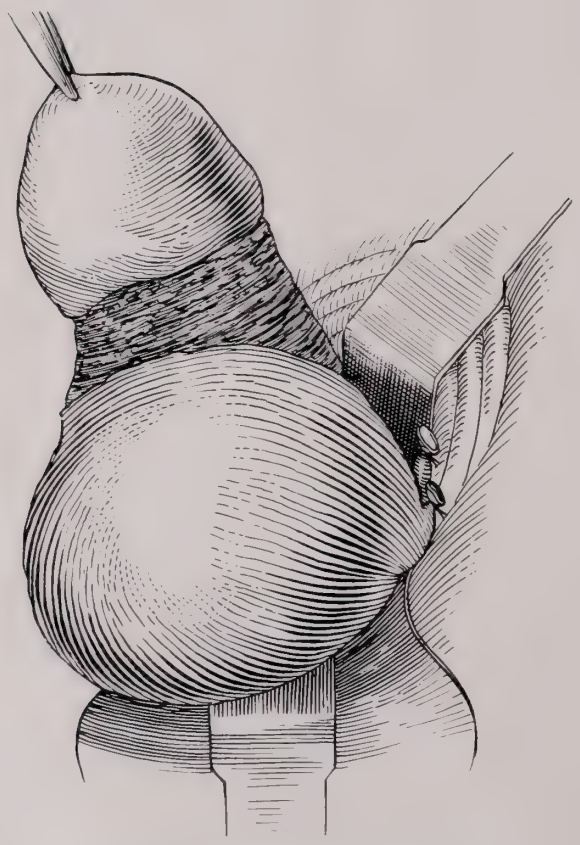


Fig. 5—Delivery of the uterus.

Closure of the Peritoneum

Excess posterior peritoneum was excised in order to eliminate the possibility of an enterocele developing. The peritoneum was closed with a purse-string suture, starting at the bladder peritoneum high up and going around, including the peritoneum of the left tube and accompanying ligaments, the broad ligaments, the uterosacral ligaments, and the peritoneum of the cul-de-sac (Figure 6). In the area of the cul-de-sac, the peritoneum was puckered with numerous small bites, continuing over to the patient's right side, including the uterosacrals and the peritoneum on up to the bladder, encircling the defect and ending at the beginning stitch. The purse-string suture was then pulled together, care being taken that the tubes and no other intraperitoneal organs were included (Figure 6). The purse-string suture was tightened with the stumps of ovarian ligaments and tubes, ready to be sutured together outside of peritoneal cavity.

Extraperitoneal Fixation of Ligaments

Next, one suture was used to bring the uterosacral ligaments together in the mid-line, incorporating the peritoneum of the cul-de-sac, and another suture to bring together the stumps of the round ligaments (Figure 6, inset). When this was done properly, all possible tied-off vessels were extraperitoneal, so that if an alarming drop in blood pressure occurred, it was almost impossible to have been due to intra-abdominal hemorrhage.

Closure of Vagina

The long sutures were cut short and any excess anterior vaginal wall was excised and then closed. If the bladder was found to be redundant and if stress incontinence had been a symptom, the bladder neck was plicated with a series of mattress sutures (Figure 7). In those cases of second and third degree prolapse where there was an excess of vaginal mucosa in the upper posterior part of the vagina, a wedge excision of this portion of vaginal wall was done. By doing this, combined with the purse-string closure of the peritoneum, the number of enteroceles and rectoceles developing postoperatively was markedly reduced. If there was generally relaxation of the entire

posterior wall, this wedge was continued down to the perineal repair, the latter being the final step.

Post-Surgical Precautions

Retention Catheter

At the completion of the operation, a Foley catheter #18 was inserted and left in place for about 60 hours. If, after its removal, the patient developed retention, the Foley was reinserted, kept in for 48 hours, and repeated several times if necessary. Also, an ordinary 4-by-4 sponge was inserted into the vagina to act as a pack to help control any oozing that might occur. This was removed in 24 hours.

Prophylactic Measures

The legs were wrapped with elastic bandages if varicosities existed. It has also been customary to follow this procedure with a daily intramuscular injection of 600,000 U of penicillin for four days.

After discharge from the hospital, all patients were instructed to douche at least once a day with a quart of warm water to which was added a tablespoonful of vinegar. They were allowed to walk stairs, bathe as they wished, but warned against straining at stool. They were examined vaginally at the office two weeks after leaving the hospital. Sloughs were removed and granulation tissue, if present, burned with the actual cautery. Office visits were repeated until the suture lines were completely healed and clean, which sometimes took up to eight weeks.

The average hospital stay was 8.2 days.

Combined Procedures

Because vaginal hysterectomy was done in a relatively short time, other procedures were occasionally combined with it, such as the following:

Inguinal hernia	7
Umbilical hernia	3
Femoral hernia	4
Hemorrhoidectomy	4
Breast biopsies	4
Thyroidectomy	1
Cholecystectomy	2

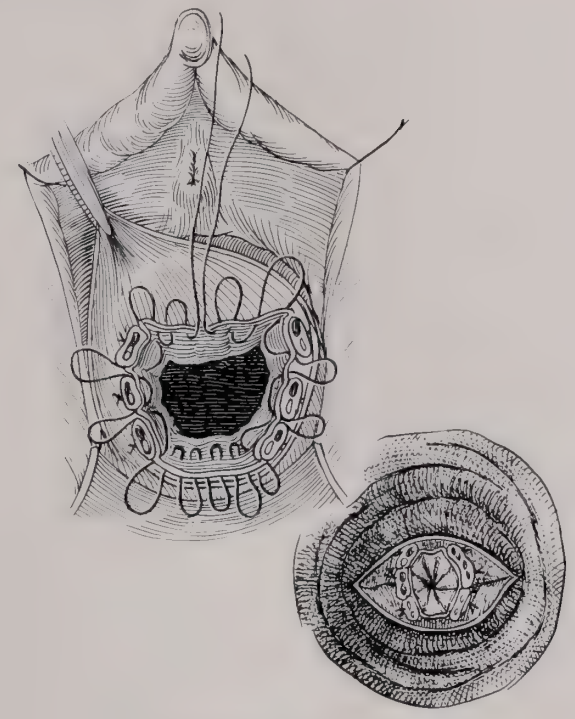


Fig. 6—Closure of the peritoneum

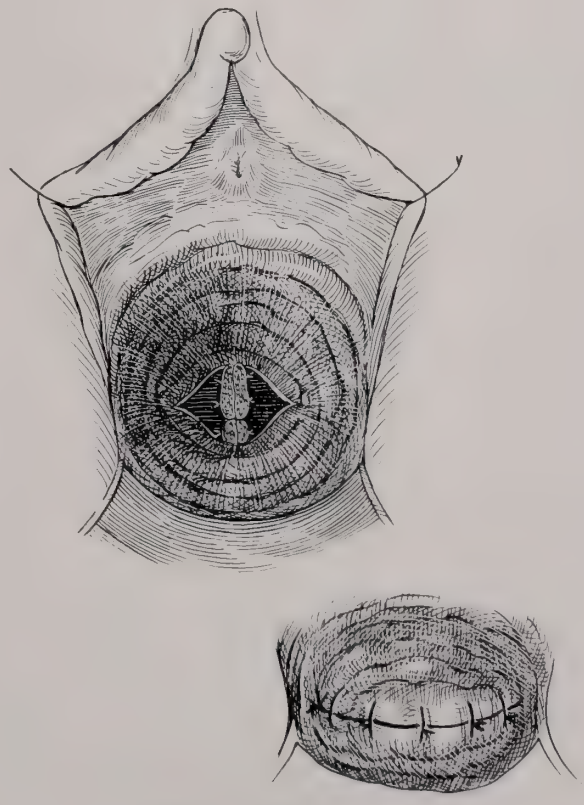


Fig. 7—Closure of the vagina

Complications Associated with Vaginal Hysterectomy

Inability to complete the operation occurred five times. The reason in two cases were large fibroids which were difficult to morcellate safely; morcellation was necessary in 33 cases. Twice the uterus was fixed to the anterior abdominal wall to such an extent that it could not be freed; and finally in one case there were so many dense adhesions from endometriosis that it seemed foolhardy to try to finish from below. In each case, repair of the perineum was completed, the abdomen entered and the uterus removed with relative ease, in no case with a prolongation of the patient's hospital stay.

In one case a sponge was lost; rather than traumatize the intestines looking for it from below, the abdomen was opened and the sponge removed. Other immediate complications were the accidental opening of the rectum in one case without any fistula formation; and the bladder was entered four times, once with a resulting vesicovaginal fistula which was successfully closed elsewhere.

Enlarged Ovaries

Oophorectomy was accomplished in 55 cases where the ovary was enlarged or diseased.

Transfusions

One hundred and fourteen (6.7%) patients required one or more transfusions. In many of these it was not because of immediate blood loss at surgery but because, prior to surgery, the patient's hemoglobin was deficient.

Postoperative Hemorrhage

Postoperative hemorrhage was a major problem and required packing or additional suture in forty-eight patients. Four times it was necessary to open the abdomen to control the hemorrhage. The high percentage of bleeding occurred in the patients under 45 years of age and seven days or more after surgery. This corresponds to the observations of Taylor and Hansen,[4] who believe that the number and severity of complications are almost directly proportionate to the youth of the patient.

Fever

One of the more numerous postoperative complications was fever. Ninety-two patients had a temperature of 102 degrees or more for two days or longer. In no case, however, was it necessary to incise or drain an abscess.

Urinary Retention

One hundred and nine patients had trouble with urinary retention, requiring further treatment with either recatheterization or re-insertion of the Foley catheter for a few days.

Miscellaneous Complications

There were three patients with non-fatal pulmonary infarcts, two with major thrombophlebitis, and one with a postoperative pneumonia. The 91-year-old patient, who had a complete procidentia and had surgery performed mainly because of her difficult custodial care, had a volvulus of the sigmoid a week after surgery and was operated upon by an associate. She survived and was discharged to live another year in comfort.

Early in this series, three gravid uteri were undetected and removed. Now all patients under 50 years of age have a pregnancy test.

There were no deaths in this series of 1700 cases. This fortunate outcome (and luck does play a role) corresponds with reports of other series of a thousand or more cases. Kempers, Hunter and Welch,[5] Andresen,[6] Hawksworth and Roux,[7] and Copenhaver[8] show a similar very low mortality rate, somewhere around 0.1%. In this series of cases, it is believed that at no time was a ureter injured.

During the same period of time, 707 abdominal hysterectomies were performed with five deaths, a mortality rate of 0.72%. Two of these deaths were due to massive pulmonary emboli, one from unknown cause or causes with a completely negative autopsy, and two from multiple complications. One of the latter patients had advanced bilateral ovarian cancer with peritoneal metastases.

Pathologic Findings

Malignancy was reported present by the pathologist forty-eight times. Of these malignancies, twenty-two were cervical carcinomas,

eight of which showed invasion; fourteen were considered in situ. Endometrial carcinoma occurred in twenty-three cases with penetration of the growth into the myometrium on fourteen occasions. One of these, a patient of 62, had had a curettage elsewhere and had been assured that no cancer existed. There were also two cases of leiomyosarcoma in fibroids, and one of sarcoma of the endometrium.

Results

Recurrence of Endometrial Carcinoma

The twenty-three cases of endometrial carcinoma have been checked within the past six months; in three there has been a recurrence. One was a frail 73-year-old woman who was operated on four years ago and died of a local vaginal recurrence one year ago. Another was a very obese patient who lived six years following the removal of her uterus for infiltrating adenocarcinoma of the endometrium and four years after a radical mastectomy for adenocarcinoma of the breast. Biopsy at laparotomy just prior to her death showed her pelvis to be filled with metastatic papillary cystadenomatous tumor tissue. The pathologist was unable to determine the primary source: uterus, breast, or ovary. The third was an obese woman of 69 who had an invasive adenocarcinoma Grade 3 and a marked prolapse. Tumor invasion of the blood vessels and lymphatics had been found at the time of surgery. She died within a year of extensive local recurrence.

These three cases of recurrence in twenty-three correspond with Pratt's[9] findings at the Mayo Clinic of 100 cases of carcinoma of the uterine fundus treated by vaginal hysterectomy with a five-year survival rate of 84%. Ingiulla and Cosmi[10] report a survival rate of 73.2% for more than five years in cases of simple vaginal hysterectomy for cancer of the corpus uteri among 112 patients so treated.

Recurrence of Carcinoma of the Cervix

Although in some of these twenty-two cases not enough time has elapsed to truly evaluate the end results, to date there has been only one recurrence, with death occurring five years after surgery. This happened early in this series, and this case was obviously poorly chosen for vaginal hysterectomy as it was a well-advanced lesion. A misinterpretation of the pathological report of the biopsy taken prior to surgery was responsible for this error.

Comments

A very careful history was always taken to be sure that the patient was not allergic to penicillin. For a while an attempt was made to do without penicillin; but, as morbidity seemed much greater without it, its use was resumed.

A late sequel, particularly in the early part of this series, was the development of an enterocele severe enough for the patient to seek surgical relief. Since the technique was changed and much more care was taken to excise the excess posterior peritoneum or enterocele sac and to close the peritoneal cavity with a purse-string suture incorporating all of the peritoneal surfaces plus the removal of a large wedge of the upper posterior vaginal wall, this complication has been markedly reduced. Stress incontinence has also been an occasional problem, and several patients have had to have a Marshall-Marchetti procedure performed upon them. Some of these women did not have this difficulty prior to surgery. Dyspareunia was an occasional complaint, but on questioning it was often found to have been present before surgery.

Conclusions

In conclusion, vaginal hysterectomy can be a procedure of very low mortality and low morbidity in the hands of a general surgeon. Sequelae such as enterocele and the development of stress incontinence have occurred; but with improved technique the number of these sequelae has been reduced. Routine pre-hysterectomy curettage is unnecessary and may at times be unwise and harmful by spreading an otherwise small and curable lesion. Finally, of all the operations a general surgeon performs, vaginal hysterectomy gives him the most satisfaction by offering the greatest relief to the largest number of patients.

References may be secured from the author or the reprints.

Cervical Cancer Detection

OVER 167,000 WOMEN have been examined and have had cervical smears done by members of the Minnesota Academy of General Practice since this project began in Minnesota in September, 1965. From these examinations, 374 cases of carcinoma have been detected. Of the thirty-nine state Academies participating in this project, Minnesota ranks fourth, with 62.6% of its members participating, and first in number of patients screened, with 167,044 out of a total of 952,573.

The project was originated in February, 1965, to demonstrate the ability of general practitioners to practice effective preventive medicine among the middle income population. The objective of the project is to prevent death and disability from cervical cancer through increasing use of cervical cytology in the office of the family physician.

Prior to 1966, only 19% of Minnesota women had one or more Pap smears. As a result of this project, 47,044 women in Minnesota and 200,000 nationally have received their first Pap smear. Some of the 952,000 women who have been examined under this project are alive today because of it. Early evidence shows that the mortality rate of 14,000 per year from cervical cancer is also being reduced. Statistics to date show the highest incidence of carcinoma in this series in the 30-34 age group, followed by the 40-44 age group and the 34-39 age group in that order. In the 15-19 year age group, six carcinomas were discovered in 11,800 examined, or an incidence of .05%.

In both the Minnesota and the national studies the incidence of carcinoma in this project is 0.3% for those having the first smear, and 0.2% for those having repeat smears. The incidence ultimately will be somewhat higher because approximately two fifths of the suspicious smears have not had a final diagnosis reported. One half of these were lost to follow-up and the other half were recorded as diagnosis pending. Because the project has been in operation only three years nationally and two and one-half years in Minnesota, no data regarding the five-year follow-up are possible.

The Committee on Cervical Cancer Detection of the Minnesota Academy of General Practice believes that the project has been rewarding in many ways. It has demonstrated that general practitioners can practice office preventive medicine and that the majority of them are willing to submit to a moderate amount of extra paper work to contribute to the furtherance of medical knowledge.

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Note: The Committee on Cervical Cancer Detection wishes to acknowledge the valuable support and cooperation received from the Cancer Control Division of the United States Public Health Service.

East Indian Count

In ancient East Indian medicine the following classification of the human body was made. It consists "of six members (the four extremities, the trunk, and the head), and has 7 membranes, 7 segments, 70 vessels, 500 muscles, 900 sinews, 300 bones, 212 joints, but only 24 nerves, and 9 organs of sense, etc. The vessels contain not only blood, but they carry also bile, mucus, and air about through the body. Of the nerves, which take their origin from the navel, 10 ascend, 10 descend, and 4 run transversely; as soon as the ascending nerves reach the heart, however, they divide into 30."*

*Baas, "History of Medicine."

Ascariasis

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VARIOUS PARASITIC DISEASES have been and are now being imported into the United States through military and civilian personnel upon their return from Southeast Asia. The most common of these diseases is malaria, followed by ancylostomiasis,† giardiasis,† and amebiasis. Our recent experience with the less common ascariasis appears to merit the attention of the physicians of this area and also to indicate a review of other complications of the disease which may confront the physician.

Case Report

A 20-year-old Marine corporal was admitted to the hospital with a twelve-hour history of crampy mid-abdominal and right upper quadrant pain, watery diarrhea and vomiting. The symptoms had followed a heavy meal. Prior to their onset the patient had experienced no gastrointestinal disturbances. He had returned from Vietnam ten months before and to his knowledge had not contacted any parasitic disease while there. He admitted, however, to having sampled native food quite frequently.

Physical examination was not remarkable. No abdominal tenderness, distention or pain was present.

Laboratory data included a hemoglobin of 15.2 gm%; the WBC was 8,300 with a normal differential count and 1% eosinophils. BUN, creatinine, 2-hr p.c. glucose and liver function tests were within normal limits. The stool examination was negative for occult blood.

Hospital course: on the second hospital day the patient passed a large number of worms in his stool. To his knowledge this had never occurred before. The worms were identified as Ascaris lumbricoides; ascaris ova were also recovered from the stools. Special stool examinations for E. histolytica and a cholecystogram were negative; the upper gastrointestinal and small bowel x-ray series revealed a heavy infestation of the jejunum with round worms (Figure). The patient was treated with Piperazine 3.5 gm by mouth on two successive days, and large numbers of adult ascarides were passed in the stool. Subsequent stool specimens were negative for ascaris ova but were positive for Giardia lamblia. Following treatment with Atabrine 100 mgm b.i.d. for five days, the *Giardia lamblia* disappeared also.

The patient was returned to duty with our recommendation that he be followed at his duty station for possible recurrence.

*From the Department of Medicine, Minneapolis Veteran's Hospital, and University of Minnesota School of Medicine, Minneapolis, Minnesota.

†See Test Your Word Score Page 1757.

Incidence

Ascariasis is estimated to parasitize 664 million people over the world[1], and together with hookworm represents more than half of all human-worm infestation[2]. Three fourths of all cases of ascariasis exist in Asia, and incidence rates for Oriental countries, Ceylon and the Philippines are reported as ranging from 15 to 79 percent of the population[3]. In rural southwest Korea there is a 90% incidence[4]; and in Cape Town, South Africa, 70% of negro children are infected with *A. lumbricoides* after the first year of life[5]. Ascariasis is commonly seen in Vietnam[6]. An estimated three million cases exist[1] in North America; highly endemic areas are the Appalachian mountains and adjacent regions, southwestern North Carolina, and south central Louisiana[3]. Under conditions of very poor sanitation virtually an entire population can be infected[6].

The Parasitic Nematodes

The largest of the parasitic nematodes, Ascaris lumbricoides is creamy-white in color with fine, circular striations on its cuticle[2]. The female is 20 to 35 cm long and about as thick as a lead pencil; the male is more slender, up to 30 cm in length, and can be distinguished by an incurved tail[7].

The Eggs

The majority of eggs require three weeks



Fig. 1. Roentgenologic examination of the gastrointestinal tract with barium contrast medium shows outlines of multiple roundworms throughout the small bowel.

for maturation. In a moist, shady habitat and moderately warm temperatures, first-stage larvae may develop in nine to thirteen days[8], while under unfavorable conditions (i.e., direct heat and excessive dryness) the eggs may remain dormant but viable for two to four years. Infection occurs by mouth, cutaneously[8].

The Larvae

After ingestion of embryonated eggs, digestive juices act on the shell, and larvae are hatched in the duodenum[7,8]. They then penetrate the duodenal wall, enter blood or lymphatic vessels, and are carried into the systemic circulation and to the lungs, where they break through pulmonary capillaries and into the alveolar spaces. There they grow, undergo two successive molts, and after ten days migrate through the respiratory passages to reach the esophagus and small intestine[3]. The worms are mature and begin laying eggs 60 to 75 days after initial ingestion of the ova[7,8]. The mature female has been estimated to produce 200,000 eggs daily[9]. Nutrients are obtained from sucking intestinal fluids. The jejunum and upper ileum are the favorite habitation sites[7].

The Invasion of the Larvae

Invasion of the larvae into the portal circulation results in mild hepatic hemorrhages; petechial hemorrhages and inflammatory changes in alveolar walls follow migration of the larvae into the alveolar spaces[3]. Simultaneous invasion of the lungs by a large number of larvae may cause a severe pneumonitis which is a form of Loeffler's syndrome[9,10].

The Clinical Symptoms

Symptoms include fever, substernal chest pain, nonproductive cough in severe cases, even hemoptysis and dyspnea[8,10]. Wheezing and musical rales are heard on examination of the lungs, and urticaria or papular skin eruptions may occur. An eosinophilic leukocytosis of 30 to 70 percent is seen in the acute phase[10]. Patchy areas of consolidation may appear on a chest roentgenogram[8]. Ascaris antigens are extremely potent sensitizing agents and will cause urticarial reactions and asthmatic symptoms in nonatopic workers employed in laboratories where ascaris worms are dissected and processed[10]. It is estimated that one sixth of ascaris-infected persons have clinical symptoms.

Organ Involvement

Another pulmonary manifestation reported is that of a solitary pulmonary nodule consisting of a granulomatous reaction surrounding ascaris eggs which were thought to have been inhaled.

Occasionally larvae reach the *general circulation* and provoke symptoms of varying severity. Lodgement of larvae in the *eye* has been associated with retinitis and palpebral edema. Penetration of larvae to the *brain* may cause convulsions, meningitis and encephalitis. Involvement of the *spinal cord* and *kidneys* may occur; and aberrant larvae may occasionally produce the visceral larvae migrans syndrome, particularly in children[8,9].

Chronic Involvement

Chronic ascariasis may be manifested by seemingly nonspecific *gastrointestinal complaints,* such as epigastric discomfort or colic, diarrhea, nausea, vomiting, low-grade fever, anorexia, and palpable abdominal mass. Weight loss and nervous symptoms such as irritability may also be present[3]. It has been reported that ascaris-infected children are physically less developed and *mentally less alert* than uninfected ones, and that nutrition and scholastic ability improve following treatment[8].

Acute Involvement

A relatively small proportion of patients develop acute ascariasis, often a complication of migration of the worms from the jejunum and ileum. Migrating worms may enter the stomach and be vomited, or they *may enter the nasopharynx and eustachian tube* or the trachea, causing suffocation. Large infestations may induce severe toxic symptoms, such as convulsions in children[8]. The most common complication of ascariasis is obstruction of the small intestine[5,12].

Medical treatment can usually prevent serious complications, but surgical intervention is necessary if medical treatment is not effective[12].

Intestinal Tract

Obstruction is usually caused by an entangled mass of worms completely blocking the

lumen. Our patient's acute episode appears to have been a partial *intestinal obstruction.* Worm secretions can provoke an inflammatory reaction in the bowel wall, and toxic decomposition products may cause *bowel wall necrosis*[5]. *Volvulus and intussusception* of the small intestine may occur [4,13] and appendicitis may develop following migration of an ascaris into the appendix[4,5].

Biliary System

Biliary obstruction has occurred, particularly in China[5] and Korea.[14] In the majority of cases, a single worm has been found in the *common duct,* but from two to 10 parasites are not unusual and from 30 to 45 ascarides have been reported.[14] Even *biliary calculi* formed from dead worms or ascaris eggs have been encountered[4,15] and may produce a clinical picture of acute cholecystitis or cholelithiasis.[3] *Hepatic abscesses* due to migration of ascarides to the liver may occur; these require surgical treatment.[16]

Pancreas

Acute *pancreatitis* may follow obstruction of the ampulla of Vater or the pancreatic duct by an ascaris. Complete, unrelenting obstruction may cause fatal *hemorrhagic pancreatitis;* but more often obstruction is temporary and the worm retreats.[3,5,8] Deep penetration of a worm into the pancreatic duct may result in formation of a *pseudocyst.*[5]

Unusual Manifestations

Other more rare complications include perforation of the intestine, bile or hepatic duct with peritonitis, diverticulitis, pleural empyema, genitourinary tract involvement and the crawling of worms out of tuberculous sinuses from psoas abscesses and from the spine.[4,8] Mesenteric infarction due to venous obstruction with mature ascarides which were thought to have developed aberrantly in the mesentery has recently been documented.[17]

Significant malabsorption from the small intestine does not occur unless tremendously large numbers of parasites are present.[18] Of 731 consecutive acute abdominal emergencies in children aged one to 12 in Cape Town, ascariasis accounted for 12.8% of the cases, ranking second only to appendicitis.[5] In that study, 37.5% of the deaths from acute abdominal emergencies were due to ascariasis. Prior to the use of Piperazine, as many as 66% of patients with intestinal obstruction due to Ascaris died, including some adults.[12]

Diagnosis

Diagnosis in routine cases depends on identification of ascaris ova in stool preparations. When pulmonary ascariasis is suspected as a cause of Loeffler's syndrome, diagnosis can be made by recovering larvae in early morning gastric aspirates,[19] or from sputum samples.[10] Hypereosinophilia is thought to appear during and shortly after the larval stages in the lung, often subsiding to near normal levels after the worms reach maturity[20] and to completely normal levels after eighteen months. Eosinophilia has been reported more prominent in children up to age 10 than in older individuals.[20] Eosinophilia occurs in up to 10% of chronic ascariasis cases; but its incidence is less than 3% in three fifths of all patients.[3] Intradermal skin tests and precipitin reactions have been employed.[21] The radiologic sign of Aiken and Dickman, "wisp-like radiolucent lines in a somewhat parallel manner with a shadow representing a mass of ascaris" seen on plain films of the abdomen, is of value in determining the etiology of acute intestinal obstruction.[12,13] Following a barium meal the worms displace the barium or barium is retained in the worms' intestinal tract after the host has evacuated the barium; this phenomenon is sometimes responsible for the incidental discovery of ascariasis.[9]

Treatment

Piperazine is the most effective drug for eradication of ascariasis.[3,8] In recommended doses it is nontoxic. When given to adults in two 3.5-gram doses 24 hours apart, cure rates approximating 95% can be achieved.[22] Ascarides are usually excreted from the first through the third day after treatment. Piperazine produces narcosis and relaxation of the worms, and they are presumably passed because of inability to maintain their position in the small intestine by pressure against the intestinal wall and resistance to intestinal peristalsis.[23] Other effective drugs are Bi-

phenium hydroxynaphthoate, Thiabenzadole[24] and Hexylresorcinol.[3]

Efforts in the control and prevention of ascariasis appear to be herculean, considering the extent of the problem. Improvement of living conditions with use of clean, sanitary toilets is essential. Where night soil is used as fertilizer, raw vegetables and fruits should not be eaten without processing. In some parts of Asia, air-borne ascaris infection is suspected.[8]

Summary

A heavy infestation with Ascaris lumbricoides was the cause of a partial intestinal obstruction in a serviceman who had returned from Vietnam 10 months prior to the onset of symptoms. The intestinal obstruction relented spontaneously and medical treatment with Piperazine succeeded in the elimination of the helminthic infestation.

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Why Does the Patient Complain

The big mistake that doctors make is in jumping from complaint to symptom; by translating in this way one makes an impersonal case out of a human being. Thus we miss several links in complaint formation. It has already been emphasized that both the patient and the doctor contribute to the manner in which the complaint is presented, and on both sides there are preconceived subconscious notions that are not clearly understood. If we wish to analyze this complicated situation, we must retrace our steps. We must realize that the question to be decided is not what sort of disease is behind the symptom the patient complains of; the real medical question is: why does the patient complain? (i.e., what is really bothering the patient?)*

*Weijel, J. A. in Richard Magraw: Ferment in Medicine, 1966.

Nobel Prize Winners In Medicine and Physiology 1956

Andre Cournand, Werner Forssmann, Dickinson Richards

"For their discoveries concerning heart catheterization and pathological changes in the circulatory system."

"In emergency conditions which menace patients by interruption of cardiac activity, such as acute collapse in cardiac patients or in anesthetic episodes and poisoning, one is forced to undertake a rapid local drug treatment. In such cases, the sole remedy is often an attempt at intracardiac injection which then occasionally can be life-saving. . . . These considerations have led me to seek a new way whereby one can penetrate into the heart without danger, and so I have investigated the probing of the right heart, approaching it from the venous system.

"After the success of experiments on cadavers, I undertook the first investigation in living humans through self-experimentation. First of all, in a preliminary experiment I allowed myself to be punctured in the right elbow vein using a large-bore needle. One of my colleagues kindly placed himself at my disposal for this purpose. I then introduced a well-oiled ureteral catheter through the cannula into the vein. The catheter was then easily introduced for a distance of 35 cm. of height. Because further catheterization appeared to my colleague to be risky, we interrupted the experiment, although I felt completely well. After one week I undertook alone a further experiment. Because venipuncture with a thick needle in oneself appeared technically too difficult, I made a venesection after local anesthesia in my left elbow and introduced the catheter without resistance for its whole length, 65 cm. This distance appeared to correspond to the path from the left elbow as far as the heart. During the introduction of the catheter, I had the feeling of gentle warmth only during the sliding along the wall of the vein, similar to the feeling during an intravenous injection of calcium chloride. By intermittent movement the catheter beat against the upper and rear wall of the clavicular vein, and I noticed an especially intense heat behind the collarbone under the insertion of the muscles of rotation of the head; at the same time, probably through irritation of vagal branches, there was a gentle cough.

"The position of the catheter was proven by x-ray and indeed I observed the tip of the catheter itself in a mirror held in front of the illuminated screen by a nurse.

"The trip from operating room to x-ray department, which is an unusually long distance in our establishment and during which I had to ascend stairs, covering the distance on foot with the probe lying in the heart, was not associated with unpleasantness. The introduction and removal of the catheter was completely painless, only being associated with the above described sensations."

Forssmann's paper describing his "probing of the heart" was published in 1929.*

A decade after Forssmann, Cournand and Richards introduced his technique into their research on the physiology of the heart and lungs, and from then on they and their colleagues demonstrated its usefulness in one brilliant study after another.†

*Werner Forssmann: Die Sondierung des rechten Herzens, 1929.
†Theodore Sourkes: Nobel Prize Winners in Medicine and Physiology, 1966.

Cutaneous Clues to Visceral Cancer*

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IN THESE DAYS of more refined laboratory techniques for diagnosis of disease, a careful examination of the skin is often overlooked as a means of determining the presence of an underlying malignant neoplasm. A possible relationship exists between certain cutaneous changes and underlying visceral cancer, lymphoma, or leukemia. In the future, more detailed information about these skin diseases may establish with greater assurance their specificity as clues to visceral neoplasms.

Arsenism

The ingestion of medicinal arsenic preparations may result in palmar and plantar hyperkeratosis, hyperpigmentation of the skin, cutaneous cancers, and sometimes even visceral carcinoma. Incidental exposure to arsenic in drinking water and in some occupations is recognized and may produce similar changes. Trivalent inorganic arsenic is usually responsible for these changes, although organic forms of the element are sometimes implicated.

A latent period, usually of several years, follows the ingestion of the arsenic before cutaneous evidence of arsenism, namely, the keratosis and pigmentation evolve. Additional time usually elapses before the accompanying visceral cancer develops. The quantity of arsenic required for these changes varies greatly from patient to patient, as does the latent period before the development of arsenical cancer.

Dermatological Findings

Keratoses developing subsequent to arsenical ingestion occur predominantly on the palms and soles although they may be found elsewhere on the body (Figure 1). Initially these are barely visible but readily palpable hyperkeratotic papules; later they become larger and verrucous,§ with surrounding callus formation. Exfoliation and fissuring of the palms and soles may also be present.

*Read at the Mid-Winter Clinical Sessions of the American Medical Association, Houston, Texas, November 28, 1967.
†Mayo Clinic and Mayo Foundation: Section of Dermatology.
‡Mayo Clinic and Mayo Foundation: Section of Medicine.
§See Test Your Word Score Page 1757.

Hyperpigmentation of the skin may accompany the hyperkeratoses as an additional sign of systemic arsenism (Figure 2). All the skin and mucous membranes may be involved, but the hyperpigmentation is more severe in areas that are usually more pigmented, namely the nipples, axillae, groin, and perineum. The pigmentation is generalized in distribution and mottled in appearance.

Dyskeratotic changes in some of these lesions may occur, resulting in ulcerating squamous-cell epitheliomas. In addition, both squamous-cell epitheliomas and superficial basal-cell epitheliomas may arise anywhere on the skin, independent of the hyperkeratoses.

Development of Neoplasia

At the same time or later, arsenical cancers involving the urogenital, oral, esophageal, and respiratory epithelia may develop.

Sommers and McManus[1] reviewed the development of cancers of the skin and internal organs in 27 patients who received injections of arsenic and found multiple skin cancers in all. In the six cases in which autopsy was done, separate additional internal cancers were found in four, three at multiple sites. In five other patients, death was ascribed to cancer; but in the absence of autopsies none were proved pathologically.

Dobson and Pinto,[2] in their study of arsenical carcinogenesis, emphasized that patients who ingest arsenic have a higher incidence of plantar and palmar keratoses. Their retrospective study considered the incidence of palmar keratosis in a group of 671 patients with cancer. They compared this incidence to the occurrence of palmar and plantar hyperkeratoses in a noncancer-bearing population matched by age and sex. In the group with cancer, 46% of the men and 26% of the women had keratosis, compared to 11% of the men and 5% of the women in the control group. A study of the histories of arsenical



Fig. 1—Arsenical keratoses on palms seen as punctate hyperkeratoses or larger hyperkeratoses that sometimes may be translucent. This patient, in addition to palmar and plantar keratoses, had a papillary, transitional cell epithelioma (grade 1) of the bladder.

ingestion of these cancer patients revealed that 13% had been exposed to arsenic as compared to 10% of the control group. This difference seemed insignificant.

These authors concluded that if arsenic is responsible for the production of palmar and plantar keratoses and if patients with internal cancer have a higher than normal incidence of palmar and plantar keratoses, then the possibility exists that arsenic is an important carcinogen for internal cancers.

Generalized Plane Xanthoma

Lynch and Winkelmann[3] have pointed out that generalized plane xanthoma, a less frequently recognized form of xanthomatous disease, is associated with other diseases of the reticuloendothelial system.

Dermatological Findings

Generalized plane xanthoma consists morphologically of yellow to yellow-brown macular areas or slightly elevated plaques that occur predominantly on the eyelids, lateral aspects of the neck, and the upper part of the trunk. The lesions may be distinct or visible only with tangential lighting. This type of xanthoma readily contrasts with papular and nodular xanthomas as seen in xanthoma disseminatum, xanthoma tuberosum, eruptive xanthoma, xanthelasma,* and xanthomas of the tendon sheaths. Some patients with generalized plane xanthoma have associated xanthelasma palpebrarum.

Plane xanthomas may be associated with other xanthomas in patients with increased blood lipid levels related to a familial pattern or with biliary cirrhosis. Generalized plane xanthoma, however, may also occur with normal lipemic serum and without the associated features previously noted.

The histologic features in plane xanthomas are distinctive but not diagnostic. Histiocytic foam cells in aggregates of only a dozen can be seen throughout the upper dermis, predominantly in a perivascular location. Giant-cell formations, atypical for Touton giant cells, may at times be striking.

Development of Neoplasia

Altman and Winkelmann[4] initially studied a group of these patients, but the relationship with systemic disease was not then apparent. Subsequently, Lynch with Winkelmann[3] documented an association between generalized plane xanthoma and diseases of the reticuloendothelial system. They reported on two patients with generalized plane xanthoma, one in whom granulocytic leukemia developed and the second in whom leukemic lymphocytic reticuloendotheliosis developed. On reviewing the literature, these authors noted that 20 patients, including their own, had generalized plane xanthoma. From the historic data, onset of the lesions occurred during childhood in four patients and during the adult years in 16. Multiple myeloma developed in six men and two women. Information was not available in all cases, but the xanthoma was recognized as being present for as long as 18 years before the myeloma was discovered. Two adult patients also had xanthomas, apparently

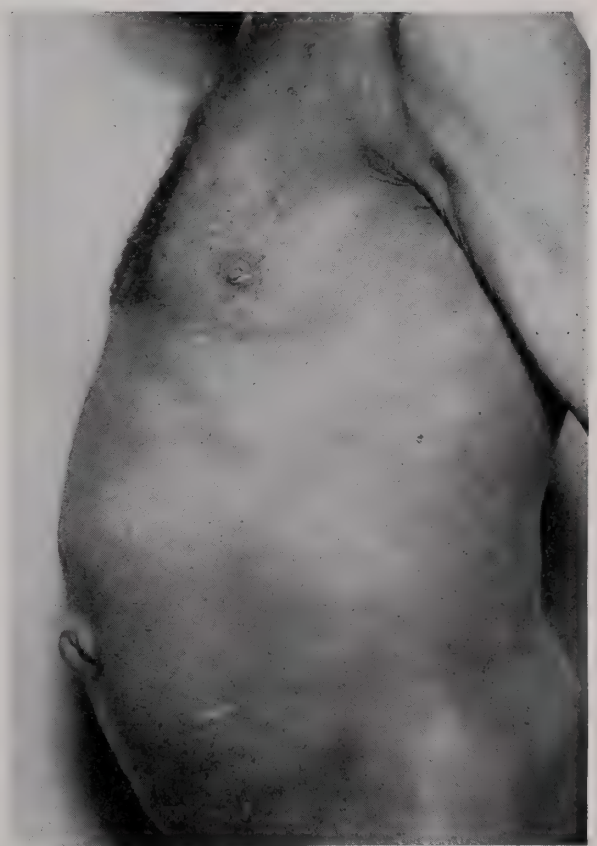


Fig. 2—Generalized hyperpigmentation, with mottled pattern and white depigmented areas, the so-called raindrop pattern that is characteristic of chronic arsenism. This patient also had cirrhosis of the liver, proved histologically, which was considered a complication of his chronic arsenic ingestion.

*See Test Your Word Score Page 1757.

present some years before discovery of their reticuloendothelial disease.

In addition to the 20 patients with typical generalized plane xanthoma, three were found with atypical, but suggestive, features of plane xanthoma. The two children of this group had leukemia and the adult, eosinophilic granuloma.

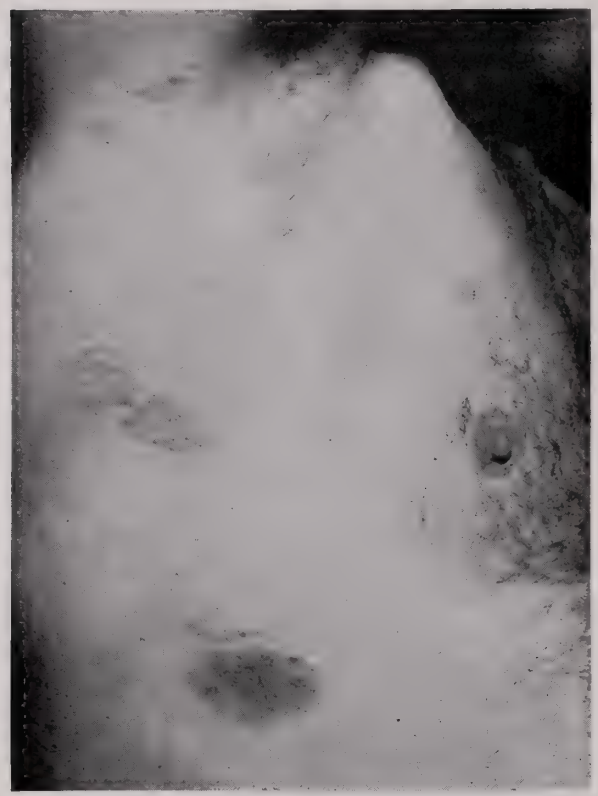


Fig. 3—This patient originally had alopecia mucinosa; later reticulum cell sarcoma developed. Note the two types of lesions, follicular papules and the erythematous plaque-form, in the same patient.



Fig. 4—Erythematous, somewhat indurated, plaques on extensors of forearms and abdomen that were associated with hair loss characterize the lesions of alopecia mucinosa in this patient.

Because 50% of the patients with generalized plane xanthoma later have systemic disease, the physician should search for multiple myeloma or leukemia in patients with these cutaneous lesions. This is particularly true when the patient is an adult, has normal blood lipids, and has no history or findings that relate his present skin findings with other xanthomatous disease.

Alopecia Mucinosa

Since 1957, alopecia mucinosa (follicular mucinosis) has been accepted as a clinical entity. Because the histologic changes were recognized as those of mucinous degeneration of the pilosebaceous unit, the name "alopecia mucinosa" was retained for this entity rather than "follicular mucinosa." Subsequently, combined evaluation of reported cases showed that many of these patients had associated lymphoreticular disease; this was particularly true in patients more than 40 years old.

Dermatological Findings

Two types of lesions are seen in alopecia mucinosa. One consists of grouped, flesh-colored to erythematous follicular papules that frequently become hyperkeratotic. This type is most often seen during childhood and represents a benign transitory disease. The second type consists of somewhat indurated, flesh-colored to red plaques, the surface of which may be somewhat scaly. This second type of lesion is most often one of the clinical features in older adults who may have associated lymphoreticular disease. Combinations of these two types of lesions may appear in the same patient (Figure 3).

Loss of hair in the involved area is the most consistent clinical feature (Figure 4). This finding is obvious when the skin lesions of alopecia mucinosa occur on body surfaces where long hair is ordinarily present. The lesions of alopecia mucinosa occur most commonly on the face, neck, trunk, and upper extremities. Local symptoms are usually minimal.

Development of Neoplasia

In 1957 it was suggested that the disease in some patients was of unknown origin and therefore "primary," whereas in others it was secondary or "symptomatic" and associated with another disease, usually reticulosis. Pinkus proposed the possibility of a virus parasitizing the follicular sheath cells as the possible cause of the follicular mucinosis. In those patients in whom the disease is benign, sufficient immunity develops so that the disease remains localized. In others, he believes that the continued stimulation of the endothelial system by the virus gradually leads to the development of lymphoma.

Ten cases of alopecia mucinosa have been studied in detail[5] at the Mayo Clinic. The lesions in two cases clinically resembled mycosis fungoides, and in one case, a histologic transition to mycosis fungoides. In three other cases, in which mycosis fungoides was seen clinically, the follicular mucinosis was considered a secondary histologic change.

Pinkus,[6] in analyzing his own cases, found that 31 of the 60 patients (52%) were more than 30 years of age and that eight of these (25%) eventually had lymphoma. More re-



Fig. 5—(*A*) Distribution of pemphigoid lesions. (*B*) Area shows blisters in bullous pemphigoid.

cently, Plotnick and Abbrecht[7] reviewed the literature and found 90 cases of alopecia mucinosa; 28 of these patients were more than 40 years old. Of this group, four had evidence of mycosis fungoides or lymphoblastoma, an incidence of 15% for this association.

Pemphigoid

A generalized blistering eruption to be differentiated from erythema multiforme, dermatitis herpetiformis, herpes simplex, and herpes zoster, and termed "pemphigoid," may occur in association with a malignant neoplasm, most often lymphoma.

Dermatological Findings

Generalized bullous pemphigoid most often involves older adults, past middle age. It consists of vesicles and bullae that predominantly involve the trunk and proximal portion of the extremities.[8] The blistering may vary from vesicles that are a few millimeters in diameter to large bullae that are several centimeters. Some may arise on an urticarial base and others on apparently normal skin. Frequently, small clusters of vesicles resembling "dewdrops" may form peripherally around erythematous plaques which are sites of previous involvement (Figure 5). Generally there are recurrent crops of lesions.

As many as 25% of the patients may have involvement of the mucosa of the oral cavity and the anogenital region. Intense pruritus and at times a burning sensation accompany the eruption.

Skin biopsy reveals a subepidermal bulla that seems to originate as a response to edema of the upper part of the dermis, elevating the epidermis.

Development of Neoplasia

An early report on pemphigoid stresses the occurrence of this disease in elderly but otherwise healthy adults.[8] Subsequent case reports indicate that generalized blistering eruptions, best classified as pemphigoid, occur with increased frequency in patients with malignant neoplasms. Our own experience would seem to confirm this.

Skog[9] reviewed the problem of the occurrence of malignant tumors in association with vesicular and bullous lesions. From his résumé of cases, it appears that the bullous eruption may have been a consequence of roentgen therapy initiated for the primary disease in three patients. In another three patients, cutaneous eruption heralded the appearance of the carcinoma. In the final three patients, the vesiculobullous eruption occurred when a metastatic disease developed.

Patients with generalized bullous eruptions not readily attributable to another cause should be examined for underlying malignant disease.

Multiple Mucosal Neuromas

As a cutaneous sign, multiple mucosal neuromas should be suggestive of a possible medullary carcinoma of the thyroid, pheochromocytoma, or both. Stimulated by the diagnostic presence of neuromas in the tongue, Gorlin and associates[10] found 17 cases in which multiple mucosal neuromas were associated with carcinoma of the thyroid or pheochromocytoma, or both. In their most recent review of thyroid carcinoma, Woolner and associates[11] noted seven patients who had findings that warranted their inclusion in this group.

Dermatological Findings

The mucosal neuromas are pink, pedunculated nodules that often first involve the tongue and labial tissues. The lips enlarge and become "blubbery" or "negroid" in appearance. In the tongue, the neuromas are characteristically situated at the tip and along the margins. In the patients seen at the Mayo Clinic, these tumors were noted early in life and became larger and more bothersome during adolescence.

The conjunctival mucosa is affected later, and the increasing size of the neuromas causes eversion of the eyelids (Figure 6). This feature, with the labial changes, produces a distinctive and characteristic facies. The buccal, gingival, laryngeal, and nasal mucosae are less frequently affected.

Development of Neoplasia

Medullary carcinoma of the thyroid was noted in seven of the 17 cases reviewed by Gorlin and associates.[10] These authors emphasized that the onset of thyroid carcinoma occurred at an early age but never before the

18th year of life. All the patients in Woolner and associates'[12] series were relatively young, the oldest being 27 years of age. This is in contrast to the high incidence of medullary carcinoma of the thyroid in patients in the sixth and seventh decades of life, when this tumor occurs independent of the other stigmata.

Pheochromocytoma was noted in seven of the 17 cases reported by Gorlin and associates.[10] Among these there was clinical evidence to indicate that this tumor may have been present in an additional three cases. In four of the seven cases the tumors were bilateral. Woolner and associates' unpublished studies[11] show that bilateral pheochromocytoma was present in five of their seven patients.

In their review, Gorlin and associates[10] emphasized the presence of a marfanoid habitus and diverticulosis in some of the patients. Woolner and associates[11] reported two patients, both with ganglioneuromatosis and diverticulosis, and still other patients with hypercalcemia, one of whom had multiple adenomas of the parathyroid gland.

The physician should be aware that firm, flesh-colored tumors of the oral and conjunctival mucosal surfaces may indeed be a clue to underlying carcinoma of the thyroid and, if associated with hypertension, perhaps also to the presence of pheochromocytoma.

Ataxia-Telangiectasia (Louis-Bar Syndrome)

Ataxia-telangiectasia is a familial neurocutaneous syndrome transmitted as an autosomal recessive trait that consists of progressive cerebellar ataxia in association with oculocutaneous telangiectasias. Malignant tumors eventually develop in some of these patients.[13,14]

Dermatological Findings

The disease has its onset early in life and is frequently first noted because of defects in station and gait as the child tries to walk. Mild spontaneous athetoid movements begin early, particularly in the upper extremities, and there is progression of these symptoms with advancing age. Patients assume characteristic postures even when sitting. Dysergia and intention tremor may develop.

The telangiectasias of the conjunctivae and skin usually appear somewhat later, although these changes have been reported to occur in children as young as two years old. The onset of these changes is more frequently delayed until the age of four to six. The bulbar conjunctivae are involved initially, with subsequent telangiectasias developing on the face, neck, and ears. The cubital and popliteal fossae may also be involved.

Clinical Manifestations

As the disease progresses, peculiar eye movements that simulate ophthalmoplegia develop. Frequent sinopulmonary infections including bronchiectasis commonly occur, and clubbing of the fingers and toes may develop. Afflicted children are often retarded in growth although their intelligence is normal. Their intelligence quotient tends to decrease on serial testing, as such tests, depending on visual coordination, become correspondingly more difficult as



Fig. 6—(*A*) Fibromas of eyelids and edema of lips which present a characteristic facies. (*B*) In this syndrome, fibromas of tongue primarily involve anterior portion.

the ocular symptoms become worse. The speech becomes slowed, slurred, and scanning, and the voice becomes weak and indistinct.

On autopsy study, the brain shows cerebellar atrophy with primary chronic, diffuse cortical degeneration.[13] Decreased numbers of Purkinje and granular cells, and to a lesser extent basket cells, are seen in the brain substance. The spinal cord is apparently not changed. Enlargement of the venules in the cerebellar leptomeninges cannot at this time be definitely related to the oculocutaneous telangiectasias. The presence then of this peculiar ataxic state, together with the oculocutaneous telangiectasias, makes the diagnosis of this condition relatively easy.

Development of Neoplasia

A number of authors have stressed the immunologic defects in these patients. Peterson and associates[15] summarized the incidence of cancer in ataxia telangiectasia and noted that of 125 patients whose cases they reviewed, two had Hodgkin's disease, four reticulum cell sarcoma, two small-cell sarcoma, and one bilateral dysgerminoma.* These authors suggested that the reticulum cell hyperplasia and the malignant neoplasms that develop in these patients may be related to the abnormal thymus.

Reed and colleagues,[14] in reporting on 22 patients in 15 family histories, revealed that many members of these families gave a history of cancer of all types, including lymphosarcoma and leukemia, in addition to diabetes mellitus and tuberculosis.

*See Test Your Word Score Page 1757.

Summary

This presentation describes the cutaneous findings in a group of relatively uncommon syndromes. We hope to challenge the clinician to critically evaluate any skin changes in patients and to consider the possibility that they may be related to a systemic disease. In the conditions enumerated, the skin changes are distinctive and should prompt the physician to suspect that a visceral cancer may be present.

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Enteritis

When the hypochondriac region is affected with meteorism and borborygmi, should pain of the loins supervene, the bowels get into a loose and watery state, unless there be an eruption of flatus or a copious evacuation of urine. These things occur in fevers.*

*Hippocrates

Cryptococcosis Presenting as an Osteolytic Rib Lesion

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Cryptococcosis, a chronic fungal disease, usually appears in an asymptomatic pulmonary form. When dissemination occurs, it is most frequently in the central nervous system, although other sites of involvement have been reported. The purpose of this report is to present a patient, who, on routine chest x-ray, was found to have an osteolytic rib lesion. She was otherwise completely asymptomatic and initially had no evidence of disease in any other site. On surgical biopsy the rib lesion was found to be due to cryptococcosis.

Case Report

This 46-year-old negro female was admitted to Mount Sinai Hospital on January 17, 1967, for investigation of an osteolytic rib lesion found on routine pre-employment chest x-ray.

Past History and Findings

The patient was first seen at this hospital in 1959 because of a persistent nodule in the left upper eyelid. She was otherwise asymptomatic, and physical examination at that time was normal. Biopsy of the eyelid nodule revealed a noncaseating granuloma consisting of epithelial cells, giant cells and lymphocytes. No further workup was done, and the patient was discharged without therapy with a tentative diagnosis of sarcoidosis.

In 1962 she had a recurrence of the eyelid nodule. At this time she was found to have cervical, axillary, epitrochlear and inguinal lymphadenopathy. The nodes were firm, smooth and nontender, varying in diameter between 3 and 5 cm. Examination of the lungs and heart was normal. Palpation of the abdomen revealed moderate hepatosplenomegaly.

Skin tests for tuberculosis, histoplasmosis, coccidioidomycosis and blastomycosis were negative. Sputum cultures for acid-fast bacilli and fungi were negative, as were blood cultures and complement fixation tests for fungi. A chest x-ray showed right paratracheal node enlargement but was otherwise negative. Cervical lymph-node biopsy showed non-caseating granulomas (Figure 1) similar to those seen originally in the eyelid nodule. Biopsy of a Kveim test (Figure 2) was considered con-

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Fig. 1—Cervical lymph node biopsy (170X) showing non-caseating granulomas.

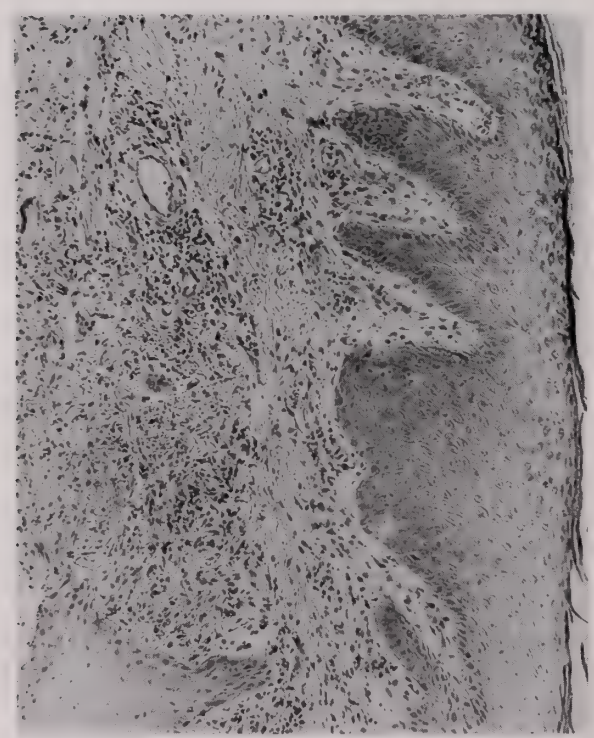


Fig. 2—Skin biopsy of the Kveim test (170X) showing non-caseating granulomas.

sistent with a diagnosis of sarcoidosis.

Present History and Findings

From 1962 until her most recent admission in 1967, the patient was entirely well. At no time did she receive steroids or other therapy. She applied for a new job in December 1966, and at that time was found to have osteolytic areas in the left third rib.

On admission the patient appeared vigorous and healthy. She was afebrile. She was again noted to have cervical, axillary, and inguinal lymph-node enlargement which did not seem to have changed since her previous admission. Examination of the lungs, heart and abdomen was otherwise negative. Chest x-rays showed at least one osteolytic lesion in the left third rib posterolaterally (Figures 3 and 4), but x-rays of the skull, clavicles, spine, hands, feet and pelvis were all negative.

Laboratory Examinations

Urinalysis negative. Hemoglobin 12.2 mg %; hematocrit 36%; RBC 3.8 million; WBC 8,870. Polys 86, lymphocytes 10, monocytes 3, eosinophils 1, basophils 0. BUN 18. Blood glucose 90 mg%. Serum electrolytes normal. Serum calcium 10 mg% and phosphorus 4 mg%. Total protein 8 gm% with albumin of 4.5 gm%. SGOT 10 units. Sedimentation rate 50 mm/hr. Serum creatinine 0.7 mg%.

A partial excisional biopsy of the involved rib was performed. Microscopic examination of this material showed a non-caseating granuloma (Figure 5), characterized by lymphocytes, histiocytes, and giant cell infiltration with PAS-positive intracellular microorganisms. Cultures of this organism were performed in three laboratories,* and the unanimous conclusion was that the organism was Cryptococcus neoformans. After surgery, sputum cultures were obtained; these also grew out fungi which on further cultural and inoculation studies had the characteristics of Cryptococcus neoformans.

Skin tests for tuberculosis, and skin and complement fixation tests for histoplasmosis, blastomycosis and coccidioidomycosis were negative. Attempts to isolate Cryptococcus from blood and urine were unsuccessful. The cerebrospinal fluid examination for electrolytes, sugar, proteins and cells was within normal limits, and also failed to grow out any organism.

The patient was considered to have disseminated cryptococcosis because of the pulmonary and rib involvement, and she was treated with Amphotericin B. After administration of 1.5 grams intravenously, the sputum cultures were negative, and involvement in the rib lesion decreased in subsequent x-ray examinations. The previously biopsied eyelid and lymph node were reviewed and re-examined for fungus, but none could be found.

Discussion

Disseminated cryptococcosis usually involves the central nervous system and is generally symptomatic. Bone involvement, which occurs

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in about 10 percent of the cases, is most often characterized by involvement of the long bones with pain, swelling and a slowly progressive course suggestive of chronic osteomyelitis. Our patient was unusual in that she had no evidence of illness except the initial asymptomatic lytic lesion in the rib. Subsequent sputum cultures were positive for Cryptococcus, but the exact origin of these organisms is difficult to determine. There was no evidence of parenchymal involvement on chest x-ray. Conceivably the Cryptococcus could have been released secondary to the surgery, or perhaps the patient had a cryptococcal bronchitis. We have no proof of the site of involvement.

In 1894 Benham cited Busse, who described the first case of cryptococcosis in a 31-year-old woman with a granulomatous lesion of the tibia which subsequently grew out the organism.[1] The bony lesions caused by Cryptococcus neoformans are usually osteolytic with slight periosteal reaction.[2] Nearly every bone has been found to be involved in the various cases reported in the literature, but there appears to be a predilection for bony prominences, cranial bones and vertebrae.[3]

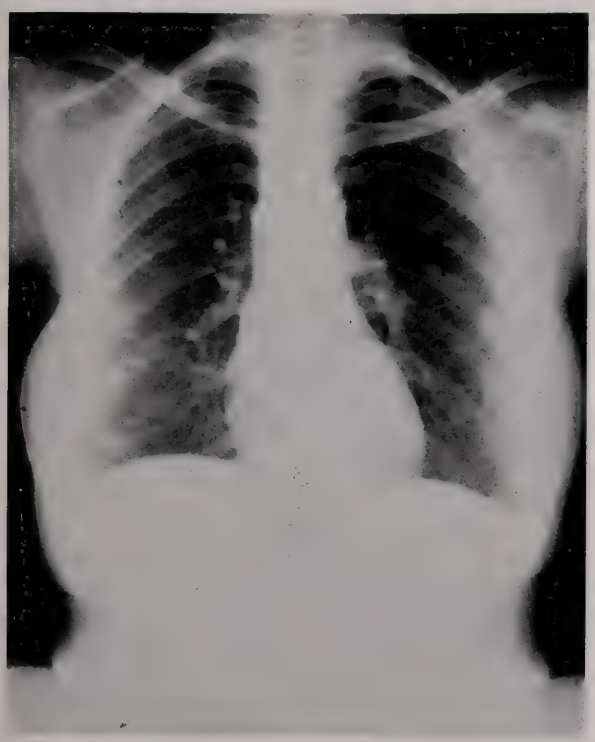


Fig. 3—Posteroanterior view of chest x-ray on admission. The arrow indicates the osteolytic lesion.

Cryptococcosis involving the ribs has rarely been described. Gosling et al.,[4] in their review of the literature of skeletal cryptococcosis, cited one case with involvement of the 10th rib reported by Dienst. Dormer et al.[5] reported a case of disseminated cryptococcosis with 9th rib involvement but with multiple bone lesions in other areas. Cryptococci may also involve the bones locally without dissemination. Our patient had isolated involvement of only one

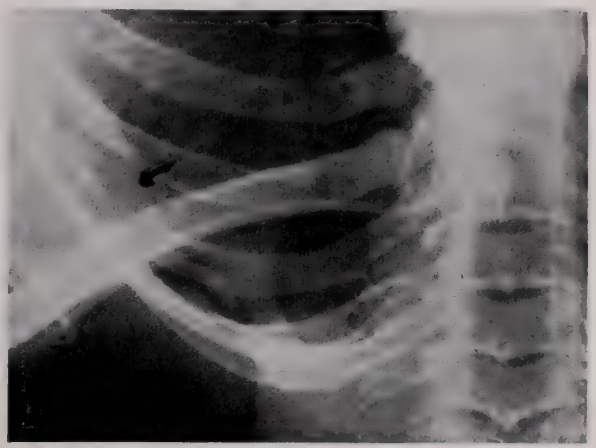


Fig. 4—Closer view of the left third rib. The arrow indicates the lesion.

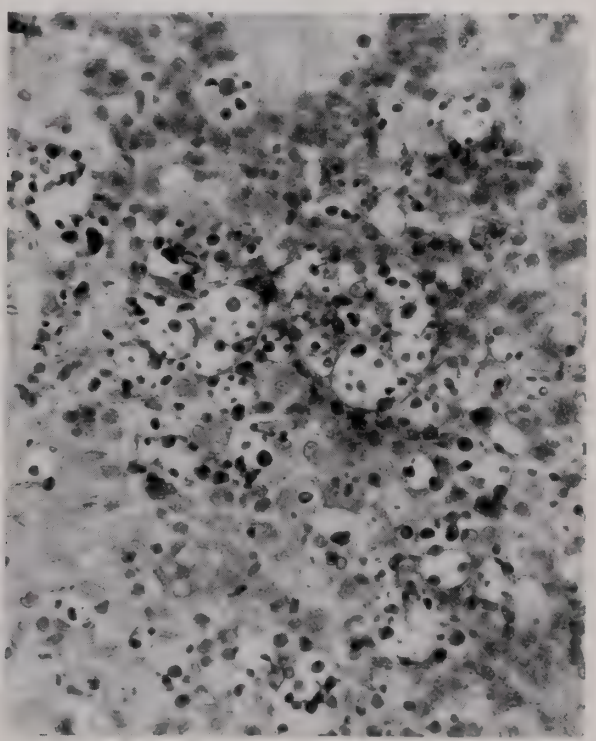


Fig. 5—Partial excisional biopsy of the third rib (periodic acid Schiff stain (450X)) showing the rounded intracellular microorganisms which have the cultural characteristics of Cryptococcus neoformans.

rib, without any evidence of bone involvement elsewhere. The only other manifestation of her cryptococcosis was positive sputum cultures obtained after surgery.

Cryptococcosis has been reported in patients with pre-existing tuberculosis,[7,8,9] leukemia,[10] other malignant diseases of the reticuloendothelial system,[11,12,13,14,22] diabetes,[15,16] and also as a complication of steroid therapy.[17,18,19] In a recent review by Harris et al. regarding the association of cryptococcosis and sarcoidosis, 11 such cases were found and an additional case was documented.[20] Symmers in 1967 mentioned five unpublished personal cases of cryptococcosis which manifested itself in the setting of sarcoidosis. Although our patient had a previous diagnosis of sarcoidosis, it is of interest that the course was an extremely indolent one and was never thought to require any form of therapy, including steroids.

Geraci[23] stated that the following are indications for treatment of cryptococcosis with Amphotericin B:

1. Progressive, diffuse, acute, subacute, chronic pneumonic, bronchopneumonic, cavitary or miliary disease, with or without pulmonary symptoms, and with positive cultures of sputum or bronchial secretion.
2. Infections associated with systemic diseases or cryptococcal infection of the central nervous system.
3. Doubtful cases in which the central nervous system shows some changes but the cultures are negative.

We elected to treat this asymptomatic disease with Amphotericin B because of the underlying systemic disease, the evidence for dissemination as manifested by the positive sputum culture, and the theoretical risk of central nervous system involvement. Our patient's sputum culture after treatment became negative, and there was improvement in the roentgenological picture of the rib lesion. She had no toxicity from the treatment and on continued follow-up has remained asymptomatic. There is no new evidence of cryptococcosis.

Summary

A patient with a long-standing diagnosis of sarcoidosis was found on routine chest film to have an osteolytic rib lesion which on biopsy proved to be due to Cryptococcus neoformans. Treatment with Amphotericin B appeared to improve the condition.

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Animal Circle

Since seven of the twelve constellations on the ecliptic represented animals, the ancients called the ecliptic the zodiac, from the Greek zodiakos (animal plus circle).

Money talks and most of us never get bored listening.—Herbert Prochnow

Multiple Endocrine Adenomatosis

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MULTIPLE ENDOCRINE ADENOMATOSIS is a syndrome characterized by: (1) tumors or hyperplasia of the endocrine glands, particularly parathyroid, pancreas, pituitary, and adrenal, (2) a very high incidence of associated peptic ulcer, (3) familial occurrence.

In their extensive review Ballard, Frame, and Hartsock[1] found that the multiple endocrine adenomatosis-peptic ulcer complex had been reported in 11 families up to 1962. Many of the individual case histories which they reviewed did not, however, provide adequate information regarding kindred. The present report documents an additional family exhibiting multiple endocrine adenomatosis. Noted here for possibly the first time is relief of the peptic ulcer diathesis† following surgical correction of the hyperparathyroid aspect of the syndrome.

Case Report

In June 1966 a 59-year-old white female was admitted for the 15th time to the University of Minnesota Hospitals, complaining of typical peptic ulcer symptoms.

Ulcer History

Her ulcer history, which dated back to 1938, included a number of upper gastrointestinal bleeding episodes and occasional spells of vomiting. In 1952 she had a 138-gram tubular resection of the stomach. Ulcer symptoms persisted following this operation and an active duodenal ulcer crater was demonstrated later in 1952, in 1953, and again in 1957. An additional segmental gastrectomy with a complementary pyloroplasty was done in 1957. At this time a 2.5-cm. round nodule removed from the hilum of the spleen proved on histologic section to be a pancreatic islet cell adenoma. During succeeding years the patient continued to complain of epigastric distress which was, however, somewhat less severe and less frequent than it had been prior to gastrectomy.

In 1964 an upper gastrointestinal x-ray examination showed a recurrent duodenal ulcer. In January 1965 she underwent gastric freezing. Following this treatment the ulcer healed with complete relief of symptoms for approximately 16 months. In April of 1966 symptoms recurred and two gastric ulcers were seen on both barium examination and gastroscopy. One of the ulcers measured

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†See Test Your Word Score Page 1757.

3 cm. in diameter and was located on the lesser curvature; the other, on the greater curvature, was approximately 1 cm. in diameter. These lesions persisted unchanged through June of 1966 in spite of rigorous medical management.

Family History

At this time the patient was first investigated for possible hyperparathyroidism. Her family history was as follows. Her father died at age 36 of upper gastrointestinal hemorrhage. A sister died at age 40 after a five-year history of ulcer disease and recurrent renal lithiasis. At postmortem examination this sister was reported to have a malignant tumor, probably originating in the pancreas. A living 62-year-old sister has mild diabetes mellitus and a long history of complicated ulcer disease which was relieved by a partial gastrectomy. On a single examination her serum calcium was 11.9 and serum phosphorus 2.0. Although she probably has hyperparathyroidism she is symptom-free and has declined operative therapy. A 32-year-old daughter has had recurrent symptoms and x-ray evidence of duodenal ulcer. Her serum calcium was 10.4 and serum phosphorus 1.9. She also has presumptive hyperparathyroidism but has permitted no further workup. Three other daughters and three brothers have exhibited no features of the multiple endocrine adenomatosis syndrome. The grandparents of this patient had no history suggestive of multiple endocrine adenomatosis. Her grandchildren are still too young to manifest the syndrome.

Laboratory Studies

Laboratory data on the patient include numerous gastric analyses between 1952 and 1966. The highest acid secretory value obtained was 18.6 mEq. of free acid in a 12-hour overnight aspiration of 1959, which is within normal limits. In 1964 a one-hour aspiration of the unstimulated stomach yielded no free acid and an eight-hour overnight aspiration provided 2.1 mEq. of free acid. Thus, although the patient had a proven pancreatic islet cell adenoma, none of the values for gastric acidity were in a range consistent with the Zollinger-Ellison syndrome. Repeated serum calcium levels ranged from 10.3 to 11.5 mg. %, serum phosphorus from 2.1 to 2.3 mg. %. Standard clearance of creatinine was 133 liters/24 hours. Tubular reabsorption of phosphorus was 83% (normal being over 85%) on a regular diet, 66% on a Bauer Aub diet. Serum alkaline phosphatase was 23 King Armstrong Units (normal less than 14 units). Skeletal x-ray examination revealed demineralization of the spine and subperiosteal reabsorption of bone in the phalanges, interpreted as characteristic of hyperparathyroidism.

Parathyroid Glands

In June of 1966 the neck was explored through a collar incision. Three of the four parathyroid glands were grossly enlarged and brownish in color and were excised. The largest weighed 4 gm. and measured 3.2 x 1.4 x 1.2 cm. Approximately half of the normal-sized fourth gland was also removed and sent to the pathologist. On histologic examination all four glands were interpreted as showing diffuse hyperplasia with loss of fat and chief cells, oxyphil cells and water-clear cells arranged in a pattern suggestive of nodular hyperplasia. No normal parathyroid tissue was identified in any of the specimens.

Following parathyroidectomy the serum calcium fell as low as 7.1 mg. % on the sixth postoperative day. The serum phosphorus at this time was 2.1 mg. %. The patient complained of some paresthesias in the limbs but was satisfactorily maintained on oral calcium and vitamin D supplements. She has continued to run a somewhat depressed serum calcium level, the last being 8.9 mg. % with a 4.2 mg. % serum phosphorus. When she neglects to take calcium supplements, limb paresthesias and circumoral numbness develop.

Ulcer symptoms disappeared immediately following surgical relief of hyperparathyroidism. Two months postoperatively the gastric ulcers had healed completely, as evidenced by both x-ray and gastroscopic examinations. During this period the patient had not followed dietary restrictions or had other medical treatment. Gastrointestinal symptoms have not recurred in the 28 months since surgical correction of the hyperparathyroidism.

This patient and her family illustrate many of the important features of the multiple endocrine adenomatosis syndrome.

Multiglandular Involvement

By definition, more than one of the endocrine glands are involved in the disease process. In addition, in any single endocrine tissue there are characteristically multiple adenomas, particularly parathyroid or pancreas. Ballard and colleagues[1] noted parathyroid adenomas in 88% of the cases reviewed and pancreatic adenomas in 81%. Also frequently involved, but not detected in this family, are pituitary (65%), adrenal (38%) and thyroid (19%) lesions.

Peptic Ulcer

Peptic ulcer has been reported in 57% of the individual cases of multiple endocrine adenomatosis. The ulcers are often multiple and atypical in locations. Characteristically the symptoms are resistant to conventional medical management and the disease is marked by frequent complications. Approximately 20% of patients with multiple endocrine adenomatosis also have the Zollinger-Ellison syndrome: ulcer disease associated with pancreatic nonbeta islet cell tumors and marked gastric hypersecretion of acid. Our patient did not have particularly high acid outputs but did have an islet cell tumor. Ulcer symptoms are the most frequent presenting complaints of patients with the multiple endocrine adenomatosis syndrome, and complications, particulary perforation, are the most com-

mon cause of death. Any patient with a strong family history of ulcer disease or marked hypersecretion of acid from the stomach should be screened for the possibility of multiple endocrine adenomatosis.

Pancreatic Pathology

Eighty-one percent of the reported patients with multiple endocrine adenomatosis had adenomas of the pancreas, usually multicentric.[1] Approximately 30% had demonstrated hypoglycemia associated with beta cell adenomas. Two thirds of patients with pancreatic lesions had nonbeta cell tumors, 25% carcinoma, 32% multiple adenomas, and 7% solitary adenoma.

Parathyroid Pathology

Parathyroid involvement in multiple endocrine adenomatosis is to be contrasted to that found in patients with primary hyperparathyroidism. Multiple parathyroid glandular involvement is the rule (68%) in multiple endocrine adenomatosis and the exception (16%) in primary hyperparathyroidism. While the majority of the multiple lesions have been called adenomas, they most probably represent diffuse hyperplasia of the parathyroid glands as described by Cope et al. in 1958,[2] rather than true adenomas. The histologic distinction between hyperplasia and adenoma depends upon finding a rim of normal parathyroid tissue with the adenoma. Our patient demonstrated hyperplastic cellular organization suggesting nodular hyperplasia.

Pituitary Pathology

Ballard and colleagues noted that pituitary adenomas were documented in 55 of their collected series of 85 patients. Almost half of these were chromophobe* adenomas. Eosinophilic hyperplasia or adenomas were associated with acromegaly in about a quarter of the patients with pituitary lesions.

Genetic Features of Multiple Endocrine Adenomatosis

Wermer, in 1954,[3] first emphasized the importance of the familial occurrence of this syndrome. He postulated that the trait is carried by a single autosomal dominant gene, which has a high degree of penetrance and expressivity. Pertinent features consistent with this thesis are that affected individuals generally have one affected parent. Approximately half of the offspring of a multiple endocrine adenomatosis parent manifest the syndrome. Normal offspring of a parent with this syndrome do not carry the trait and therefore have normal children.

Discussion

As noted above, the most frequent presenting complaint of patients with multiple endocrine adenomatosis is secondary to peptic ulcer disease. It is probably not practical to screen all patients with ulcer for hyperparathyroidism, but certainly those with a strong family history, intractable disease, extreme hyperacidity, or patient or family history of renal stones should be carefully investigated for the possibility of concurrent hyperparathyroidism and for other endocrine tumors. In addition, a patient or family history of hypoglycemic attacks, acromegaly, adrenal or thyroid adenomas should also suggest the possibility of this syndrome. Primary hyperparathyroidism is allegedly associated with an increased incidence of peptic ulcer disease. Characteristically these ulcers are chronic, recurrent, and recalcitrant to medical management.

Wilder and colleagues,[5] reviewing this association, concluded that the great majority of patients obtain definite relief from the ulcer diathesis following parathyroid surgery. This has apparently not been the case with multiple endocrine adenomatoses and ulcer disease. Wermer[4] suggested that the ulcer is an independent manifestation of the syndrome rather than secondary to hyperparathyroidism. If his contention is correct, one would anticipate that relief of hyperparathyroidism would not alleviate the ulcer diathesis. The patient reported in this paper experienced healing of ulcers and definite disappearance of symptoms for approximately two years following relief of hyperparathyroidism. We would therefore conclude that correction of hyperparathyroidism may provide relief of ulcer symptoms in patients with multiple endocrine adenomatosis.

*See Test Your Word Score Page 1757.

Summary

Multiple endocrine adenomatosis is a syndrome characterized by multiple tumors of the endocrine tissues and a high incidence of peptic ulcer. A family is reported which exhibits many of the features of this syndrome, including hyperparathyroidism, ulcer disease, and pancreatic tumors. The patient presented was completely relieved of ulcer symptoms by surgical correction of hyperparathyroidism.

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London Doctors

Your modern London doctor has many advantages denied to his predecessors. There is the National Health Service, which is going to be quite wonderful if once we can get over the first twenty years of teething troubles. . . . There are medical films and medical films. The former for teaching purposes and the latter for the greater glory of Wardour Street and the benefit of the box office.

London has wonder-drugs and wonder-machines often big enough and bright enough to obscure completely the patients they are intended to benefit. It has medical schools and teaching hospitals which are among the wonders of the world and it has some out-patient waiting-rooms that would have made Rowlandson blench.

There are in London some clinics that have attracted distinguished doctors from all over the world. Just around the corner from one of them and masquerading under a medical title is one of those places where brides-to-be can have all the exercise and massage needed to take their hips down a little.

Wherever you go in London you meet doctors. Wherever doctors go they meet other doctors. At their medical societies, in hospitals, in clubs, and all over the place doctors disagree profoundly about almost everything. There is only one thing they have in common. For forty-nine different reasons they would all rather live and work in London than anywhere else in the world.*

*Harvey Graham: A Doctor's London, 1952.

Turmoil on the Drug Scene

"Americans are now paying the greatest price they have ever paid for worthless nostrums, ineffectual and potentially dangerous devices, treatments given by unqualified practitioners, food fads and unneeded diet supplements, and other alluring products or services that make misleading promises of cure or end to pain.

"It is incredible that a wealthy nation, priding itself on its enlightenment and its thirst for progress, should pay such a heavy penalty for ignorance or lack of adequate enforcement."

*James Harvey Young: The Medical Messiahs: A Social History of Health Quackery in Twentieth-Century America, 1967.

—Report of the Williams Subcommittee, 1965.*

Blood Gas Monitoring of Patients in Respiratory Failure

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THE INTERRELATIONSHIP of ventilatory function, carbon dioxide tension (P_{CO_2}), oxygen tension (P_{O_2}), and hydrogen ion concentration ($[H^+]$) must be appraised in each clinical situation in which there is alveolar hypoventilation with associated respiratory acidosis. Impairment of ventilation can produce respiratory acidosis with superimposed metabolic alkalosis or metabolic acidosis. Appropriate treatment of respiratory failure requires an awareness of the mechanism producing the ventilatory impairment and reasonable quantitation of the resulting chemical abnormalities in the blood. As treatment proceeds, these chemical derangements can change quickly, so that frequent reappraisal is required. Compensatory changes complicate the problem.

The basic concepts in the physiology of respiratory acidosis can be understood better if considered in the form of equations.

Ventilation Equation

$$P_{aCO_2} = 0.864 \frac{\dot{V}_{CO_2}}{\dot{V}_A}. \qquad \text{(equation 1)}$$

The arterial CO_2 tension (P_{aCO_2}) depends on the quotient of the rate of metabolic production of carbon dioxide ($\dot{V}_{CO_2}$) divided by the rate of removal of carbon dioxide from the blood by the lungs as measured by the rate of alveolar ventilation ($\dot{V}_A$ = total ventilation minus dead space). The metabolic production of carbon dioxide increases in relation to rest in some conditions (such as exercise, fever, and hyperthyroidism) and decreases in others such as hypothyroidism. Hypoventilation and hyperventilation are defined on the basis of the resulting P_{aCO_2}, so that by monitoring this parameter we can determine if alveolar ventilation is appropriate to clear the CO_2 being produced by the body's metabolic processes.

*Mayo Clinic and Mayo Foundation: Section of Medicine.

Acid-Base Equation

The hydrogen ion concentration in plasma is given by:

$$[H^+] = 24 \times \frac{P_{CO_2}\ \text{(Lungs)}}{[HCO^-_3]\ \text{(Kidney)}}. \qquad \text{(equation 2)}$$

The acid-base equation pertains to the regulation of acid-base balance and is a simplified form of the Henderson-Hasselbalch equation. It can be thought of as:

$$pH = \frac{[HCO^-_3]\ \text{(renal regulation)}}{H_2O + CO_2\ \text{(ventilatory regulation)}}.$$

The numerical constant used in the acid-base equation is appropriate for blood plasma[1] when hydrogen ion concentration ($[H^+]$) is measured in nanoequivalents (equivalents per liter $\times 10^{-9}$), bicarbonate ion concentration ($[HCO^-_3]$) in milliequivalents per liter, and carbon dioxide tension in millimeters of mercury. Dissolved carbon dioxide combines with water to form carbonic acid. Thus, if effective alveolar ventilation is reduced and carbon dioxide tension (P_{ACO_2}) increases, the hydrogen ion concentration will increase but the bicarbonate concentration in the plasma will remain constant. However, if the carbon dioxide tension remains increased, the kidneys will compensate by retaining bicarbonate. If the carbon dioxide tension and bicarbonate concentration increase proportionately, the hydrogen ion concentration will be normal even though the carbon dioxide tension is high; this is compensated respiratory acidosis. In chronic obstructive pulmonary disease, carbon dioxide tension can increase faster than compensation can be achieved through renal adjustment; thus the hydrogen ion concentration increases (pH decreases) and respiratory acidosis is produced.

Oxygenation Equation

The third equation (the alveolar gas equation) deals with the alveolar oxygen tension (P_{AO_2}):

$$P_{AO_2} = P_{IO_2} - P_{ACO_2}\left(F_{IO_2} + \frac{1 - F_{IO_2}}{RQ}\right), \qquad \text{(equation 3)}$$

in which P_{AO_2} = alveolar P_{O_2} (mm Hg); P_{IO_2} = P_{O_2} of inspired air (mm Hg); P_{ACO_2} = alveolar P_{CO_2} (mm Hg); F_{IO_2} = fraction (%) of O_2 in inspired air; and RQ = respiratory exchange ratio. The respiratory exchange ratio (RQ) is the ratio between metabolic output of CO_2 and metabolic uptake of O_2 and varies between 0.7 and 1.0. Usually, the RQ is less than 1.0 in the steady state.[2,3]

$$RQ = \frac{\dot{V}_{CO_2}}{\dot{V}_{O_2}}. \qquad \text{(equation 3a)}$$

If R = 1, then $P_{AO_2} = P_{IO_2} - P_{ACO_2}$.

More simply, the oxygenation equation states:

Arterial oxygen tension (P_{aO_2}) = inspired air P_{O_2} minus alveolar P_{CO_2}. In respiratory acidosis with CO_2 retention, the partial pressure of oxygen in the alveoli may be significantly reduced as shown by the relationship in the following example:

Normal: P_{AO_2} (110 mm Hg) = P_{IO_2} (150 mm Hg) − P_{ACO_2} (40 mm Hg).

Respiratory acidosis: P_{AO_2} (60 mm Hg) = P_{IO_2} (150 mm Hg) − P_{ACO_2} (90 mm Hg).

The latter relationship demonstrates why there is a decrease in alveolar oxygen tension when there is an increase in the arterial carbon dioxide tension.

Pulmonary Alveolar-Arterial Oxygen Gradient

The net pulmonary alveolar-arterial oxygen gradient is the difference between the alveolar and arterial oxygen tensions. This gradient is several millimeters of mercury greater than would be anticipated. The gradient exists as a result of diffusion limitation in the alveolar membrane and shunting of deoxygenated blood to the left heart by way of underventilated alveoli or via bronchial veins. The partial pressure in the alveolus (P_{ACO_2}) is equal to the partial pressure in arterial blood (P_{aCO_2}) because there is no significant diffusion gradient of carbon dioxide. Thus, as shown in the preceding paragraph, it becomes possible to calculate average alveolar oxygen tension from a knowledge of the oxygen tension in the inspired air, the respiratory quotient, and the arterial carbon dioxide tension.

How can we obtain meaningful information in critically ill patients with respiratory failure? Alveolar samples are difficult to collect

in patients requiring assisted ventilation, and our data are derived either from the Astrup determination which utilizes arterialized capillary or venous blood or from direct measurements of arterial blood by the use of pH, P_{CO_2}, and P_{O_2} electrodes. Fortunately, the P_{CO_2} in the alveolar gas is the same as the arterial P_{CO_2}, since no significant diffusion gradient exists for carbon dioxide. Thus, given the value for alveolar P_{CO_2} and the oxygen tension of inspired air (150 mm Hg) and being able to estimate the RQ, we can estimate the expected alveolar P_{O_2}. It should be noted that marked discrepancies between the expected values and the measured values are usually due to changes in the physiologic dead space.

The Astrup technique[4,5] was cleverly devised to estimate the carbon dioxide tension of the blood from readings with a pH meter only. It is accurate for measuring pH and P_{CO_2} if blood is drawn, stored, and analyzed properly. If the determination is made on venous blood from a patient who is critically ill with low cardiac output or metabolic acidosis, the results may lead to serious error. It is important to note that this technique gives no information regarding the state of oxygenation of the blood. Hypoxia for any reason, such as alveolar hypoventilation or conditions giving rise to an abnormal alveolar-arterial oxygen gradient, requires direct measurements of the arterial oxygen tension, carbon dioxide tension, and pH for proper assessment.

Normally, the respiratory center is very sensitive to changes in arterial carbon dioxide tension. However, when the arterial carbon dioxide tension increases to a value (variable with each person) greater than 65 mm Hg, the respiratory center becomes less sensitive to carbon dioxide. As a result, hypoxia may become the main stimulus to respiration, through aortic and carotid chemoreceptors. When a patient with chronic obstructive pulmonary disease is given oxygen in a sufficient concentration to increase the arterial oxygen concentration, the stimulus is removed. As a consequence, ventilation and the rate of elimination of carbon dioxide decrease (Equation 1). Then, carbon dioxide concentration increases in the blood, the carbonic acid concentration increases, the hydrogen ion concentration increases (Equation 2), the pH decreases, respiratory acidosis becomes more profound, and coma and death may occur. This situation shows clearly the interrelationships of the three equations and the impossibility of altering one without affecting the other two. Oxygen can be given to increase the oxygen tension if the patient is being adequately ventilated or if he is stimulated to breathe more deeply. This type of acidosis will disappear if the patient blows off the carbon dioxide. Treatment with bicarbonate or tris-(hydroxymethyl)-aminomethane (THAM) may then be deferred unless the pH remains dangerously low (less than 7.20) as the carbon dioxide tension approaches normal.

The three equations are helpful in understanding the alterations in acid-base balance which can lead to derangements in respiration and circulation. Increased airway resistance requires increased respiratory work to maintain the same level of alveolar ventilation, and results in increased metabolic production of carbon dioxide. A decrease in pH leads to pulmonary arterial vasoconstriction (pulmonary hypertension) and further sensitizes the lung to the vasoconstriction caused by hypoxia.[6-8]

The interrelationships of ventilation, carbon dioxide tension, oxygen tension, and hydrogen ion concentration are illustrated by the following seven cases (three of chronic obstructive pulmonary disease, three of diffusion abnormalities, and one of primary alveolar hypoventilation).

Case Reports

Case 1.

A 52-year-old farmer was examined because of shortness of breath of six years' duration; he had been unable to work for two years. He had smoked cigarettes (one pack daily) for 30 years.

On examination he had marked hyper-resonance with absence of breath sounds over the upper part of the thorax and grade 4 (on the basis of 0 to 4) expiratory slowing. A clinical diagnosis of chronic obstructive pulmonary disease with marked bullous disease was made.

A thoracic roentgenogram showed severe bullous emphysema with blebs and marked compression of the lower lobes. A lung scan confirmed the absence of perfusion except in the lower lobes. A pulmonary angiogram confirmed the compression of vasculature from the large bullous sacs. An electrocardiogram was normal.

Pulmonary function studies demonstrated a severe obstructive pattern: maximal breathing capacity, 33 liters/min; maximal midexpiratory flow rate, 0.2 liter/sec; and

nitrogen washout index, 7.7%. The oxygen saturation decreased from 98 to 91% after five minutes of exercise. The carbon monoxide diffusing capacity was 11 ml/min/mm Hg (normal for the patient was estimated to be 22 to 32 ml/min/mm Hg).

Results of arterial gas studies and an Astrup determination[4,5,9] are shown in the Table.

Comment

In Case 1 there was chronic obstructive pulmonary disease due to marked compression of remaining lung tissue by huge bullous areas. Blood was being shunted (alveoli poorly ventilated but adequately perfused), accounting for the low arterial oxygen tension. An operation was performed to resect the huge pneumatocele and relieve the compression of the left lower lobe and the problem of poor alveolar ventilation expressed functionally as pulmonary arteriovenous admixture.

Case 2.

A 52-year-old man was admitted because of shortness of breath and edema of six months' duration. He had smoked for 35 years and had a long history of chronic cough and sputum production. The diagnosis was chronic obstructive pulmonary disease with chronic bronchitis, cor pulmonale, and congestive heart failure. He had hypercapnia, hypoxemia, and polycythemia on admission. An electrocardiogram showed right axis deviation. A thoracic roentgenogram revealed cardiomegaly, pulmonary congestion, and a right pleural effusion. On thoracentesis, 1,300 ml of fluid was removed from the right side. Blood gas and Astrup values are listed in the Table.

Case 3.

A 49-year-old man was transferred here from another hospital; he had marked shortness of breath, chronic cough and sputum production, and profound congestive heart failure. He was hypoxemic, hypercapneic, and polycythemic on admission. A thoracic roentgenogram showed marked pulmonary vascular congestion, cardiac enlargement, pulmonary fibrosis, and bilateral pleural effusions. An electrocardiogram showed a right axis deviation, a prominent P wave in lead V_1, and right ventricular hypertrophy. Pulmonary function studies one year earlier had shown a marked obstructive pattern: maximal breathing capacity, 17 liters/min, maximal midexpiratory flow rate, 0.3 liter/sec, and nitrogen washout index, 17%. Blood gas and Astrup values are listed in the Table.

Comment

Cases 2 and 3 are examples of chronic obstructive pulmonary disease with chronic bronchitis. With infection and secretions obstructing the distal bronchi, areas of lung are being perfused but not adequately ventilated and shunting is occurring, accounting for low arterial oxygen tensions. In both cases the patients had been taking thiazide diuretics and both had low potassium and chloride values, resulting in a metabolic alkalosis superimposed on a chronic respiratory acidosis. Therapy was aimed at improving alveolar ventilation with intermittent positive-pressure breathing, decreasing airway obstruction with bronchodilators, and correcting the hypoxemia with nasal administration of oxygen at 2 liters/min. Potassium chloride was given to correct the electrolyte abnormality.

Case 4.

A 58-year-old woman was admitted to the hospital because of shortness of breath of three months' duration. She had had a right radical mastectomy several years prior to this for grade 3 adenocarcinoma; axillary nodes had been involved and she had been given cobalt treatments postoperatively. She was dyspneic, cyanotic, and hyperventilating. A thoracic roentgenogram showed lymphangial metastases. The diagnosis was diffusion abnormality on the basis of lymphangial carcinomatosis. An electrocardiogram showed a sinus tachycardia. Blood gas and Astrup values are listed in the Table.

Case 5.

A 28-year-old housewife was admitted because of massive gastrointestinal bleeding of three days' duration. An emergency operation was necessary because of inability to keep up with blood replacement over 24 hours. She had a history of Raynaud's disease and dysphagia, and a diagnosis of scleroderma seemed likely on the basis of the appearance of her face and hands. Four days later, she aspirated gastric contents and became markedly cyanotic with acute respiratory distress. We postulated that the profound hypoxemia was related to aspiration pneumonitis superimposed on a diffusion abnormality from pulmonary scleroderma. Blood gas and Astrup values are listed in the Table.

Case 6.

A 60-year-old woman was admitted with marked shortness of breath and rapid heart rate of three months' duration. A left radical mastectomy had been performed for carcinoma of the breast one year before and she had received radiation therapy postoperatively because of involvement of axillary nodes. She had been well until three months prior to this hospitalization. A thoracic roentgenogram showed diffuse lymphangial spread throughout both lung fields. An electrocardiogram showed a sinus tachycardia. Blood gas and Astrup values are listed in the Table.

Comment

Cases 4, 5, and 6 are examples of diffusion abnormalities with arterial hypoxemia and hyperventilation. These three patients likewise had low arterial oxygen tension, indicative of abnormal diffusion; the fact that in Cases 5 and 6 there was no return of arterial oxygen saturation to normal when the patient was breathing 100% oxygen is evidence of abnormal shunting in addition to the abnormal diffusion.

In Cases 4 and 6, oxygen was given by nasal cannula at 5 liters/min to compensate for the alveolar-capillary block. In Case 5, oxygen at 3 liters/min was administered to improve diffusion, but intermittent positive-pressure breathing, expectorants, and induction of coughing also were used to correct the atelectasis that was resulting in areas being perfused but not adequately ventilated.

Case 7.

A 61-year-old obese woman (60 inches, 209 pounds) was admitted with cyanosis, polycythemia, and dyspnea of approximately eight years' duration. She had had numerous phlebotomies during the preceding eight years with only temporary relief of her symptoms. Cyanosis

had been present for approximately four years. The thoracic roentgenogram showed mild cardiac enlargement; the lung fields were clear. Pulmonary function studies revealed mild expiratory slowing. Arterial gas studies showed significant arterial oxygen desaturation and hypercapnia, both of which improved with voluntary hyperventilation of room air (Table).

Comment

Case 7 is an example of alveolar hypoventilation associated with obesity (the Pickwickian syndrome). Ventilatory and diffusion capacities were normal; however, arterial hypercapnia and hypoxia developed, presumably because of failure of the respiratory center to detect these abnormalities. With voluntary hyperventilation, these values returned to normal.

Discussion

The Table compares values from arterial blood gas studies with the Astrup values. In many cases of respiratory failure it is necessary to know oxygen tensions as well and to have more complete information available by direct electrode measurement of the pH and carbon dioxide and oxygen tensions of an arterial blood sample. When there is an arteriovenous fistula, abnormal shunting, or primary alveolar hypoventilation, direct measurements of the arterial oxygen and carbon dioxide tensions should be performed. Comparison of the data demonstrates that, in three of the six cases of abnormal shunting and profound depression of the arterial oxygen tension, monitoring acid-base balance by Astrup determinations would not provide adequate data. Venous carbon dioxide tension is normally about 7 mm Hg higher than arterial carbon dioxide tension.

The Astrup determination indicated a compensated respiratory acidosis in Cases 1, 2, and 3. However, the normal arterial carbon dioxide tension indicated that respiratory failure did not exist but rather that there was a severe respiratory disturbance manifested as arterial hypoxemia. The treatment of the respiratory alkalosis in Case 5 could not be guided by Astrup determinations alone because of the areas of lung being perfused but not ventilated, resulting in the low arterial oxygen tension.

The most important consideration in treatment is the realization of the interrelationships of oxygen tension, carbon dioxide tension, and hydrogen ion concentration in each case of respiratory failure. Direct arterial blood gas measurements are more reliable than are Astrup determinations in following the course of a patient in respiratory failure. The technique of arterial puncture is simple but cannot be relegated to the average laboratory technician. In smaller hospitals where arterial blood gas determinations are not available,

TABLE
SUMMARY OF ARTERIAL BLOOD GAS AND ASTRUP DATA

	Arterial blood gas determinations				Astrup determinations				
Case	P_{aO_2} (mm Hg); normal, 80-100	P_{aCO_2} (mm Hg); normal, 36-44	pH; normal, 7.36-7.44	Oxygen saturation (%); normal, 95-98	P_{CO_2} (mm Hg); normal, 36-42	pH; normal, 7.38-7.42	Standard bicarb. (mEq/liter); normal, 22-26	Base excess (mEq/liter); normal, +2.5 to —2.5	Buffer base (mEq/liter)*
1	58	42	7.41	94	67	7.38	27.2	4.0	52
2	54	43.5	7.46	90	63	7 38	30.8	8.0	56.6
3	42	54	7.5	83	62	7.48	40	11.8	67
4	55	31	7.46	90 (with O_2, 6 liters/min)	40	7.42	25.6	2.2	50
5	42†	27	7.54	80	38	7.50	28.8	6.0	52.0
	184‡	39	7.46	100	28	7.56	31	8.7	57.8
6	50	36	7.45	86	38	7.42	23	.8	46
7	50	58	7.39	80					
	75§	44	7.47	95					

*Normal = 41.6 + 0.42 × hemoglobin concentration in gm/100 ml.

†The data in this line were obtained on Feb. 13, 1967.

‡The data in this line were obtained on Feb. 23, 1967, while the patient was breathing 100% oxygen. Normal values under these conditions are 610 to 670 mm Hg.

§The data in this line were obtained after the patient had hyperventilated room air for 1 minute.

monitoring can be achieved with the Astrup technique[5] in cases of respiratory acidosis when abnormal shunting is not evident. Assessment of pH, carbon dioxide tension,[10] and the metabolic component of acid-base disturbance can be made with the Astrup technique, but information regarding oxygenation of the arterial blood must be estimated on a clinical basis.

Each patient with respiratory insufficiency should be observed at frequent intervals. If this is not possible, the patient should be transferred to a hospital with a respiratory care unit where 24-hour monitoring of blood gases and ventilation is possible. It is essential to know the severity of respiratory acidosis and whether it is complicated by metabolic (diabetic, renal, or lactic) acidosis or a metabolic (due to hypokalemia) alkalosis. Monitoring is essential during mechanical ventilation in chronic respiratory acidosis to prevent too rapid correction of the hypercapnia with the development of subsequent alkalosis and its consequent cardiac arrhythmias and central nervous system disorders.[11]

Case 7 is an example of primary alveolar hypoventilation in the obese[12,13] and demonstrates the usefulness of arterial gas studies not only in pinpointing the gas derangements but in establishing a diagnosis.

Summary

The interrelationship of ventilatory function, carbon dioxide tension, oxygen tension, and hydrogen ion concentration must be appraised in each clinical situation in which there is alveolar hypoventilation and respiratory acidosis. Treatment depends upon complete knowledge of acid-base abnormalities and careful monitoring of ventilation and blood gases. Cases are presented to show that, when hypoxia is related to alveolar hypoventilation or shunting of blood, data obtained from Astrup determinations do not provide adequate information without knowledge of arterial oxygen tensions.

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Warnings—Watch for the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, retinal thrombosis); if present or suspected discontinue the drug immediately.

British studies reported in April 1968[1,2] estimate there is a seven- to tenfold increase in mortality and morbidity due to thromboembolic diseases in women taking oral contraceptives. In these controlled retrospective studies, involving 36 reported deaths and 58 hospitalizations due to "idiopathic" thromboembolism, statistical evaluation indicated that the differences observed between users and non-users were highly significant. The conclusions reached in the studies are summarized in the table below:

Comparison of Mortality and Hospitalization Rates Due to Thromboembolic Disease in Users and Non-Users of Oral Contraceptives in Britain.

Category	Mortality Rates		Hospitalization Rates (Morbidity)
	Age 20-34	Age 35-44	Age 20-44
Users of Oral Contraceptives	1.5/100,000	3.9/100,000	47/100,000
Non-Users	0.2/100,000	0.5/100,000	5/100,000

No comparable studies are yet available in the United States. The British data, especially as they indicate the magnitude of the increased risk to the individual patient, cannot be applied directly to women in other countries in which the incidences of spontaneously occurring thromboembolic disease may differ.

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or sudden onset of proptosis, diplopia or migraine. Withdraw medication if papilledema or retinal vascular lesions are found.

Since the safety of Ovulen in pregnancy has not been demonstrated, it is recommended that pregnancy be ruled out for any patient who has missed two consecutive periods before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the first missed period.

A small fraction of the hormone agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

Precautions—Pretreatment physical examination should include special reference to the breasts and pelvic organs, and a Papanicolaou smear.

Endocrine and possibly liver function tests may be affected by Ovulen. Therefore, it is recommended that such tests if abnormal be repeated after the drug has been withdrawn for two months.

Pre-existing uterine fibromyomas may increase in size under the influence of progestogen-estrogen preparations.

Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

In breakthrough bleeding, and all irregular vaginal bleeding, consider nonfunctional causes. Adequate diagnostic measures are indicated in undiagnosed vaginal bleeding.

Carefully observe patients with a history of psychic depression and discontinue the drug if severe depression recurs.

Any possible influence of prolonged Ovulen therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study.

A decrease in glucose tolerance has occurred in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be observed carefully while receiving Ovulen.

Because of the effects of estrogens on epiphyseal closure Ovulen should be used judiciously in young patients in whom bone growth is not complete.

The age of the patient constitutes no absolute limiting factor, although Ovulen therapy may mask the onset of the climacteric.

The pathologist should be informed of Ovulen therapy when relevant specimens are submitted.

Adverse Reactions—A statistically significant association has been shown between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: cerebrovascular accidents, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, breast changes (tenderness, enlargement, secretion), change in weight, changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post partum, cholestatic jaundice, migraine, allergic rash, rise in blood pressure in susceptible individuals, mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme and nodosum, hemorrhagic eruption, itching.

The following laboratory results may be altered by oral contraceptives: hepatic function: increased sulfobromophthalein and other tests; coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X; thyroid function: increase in PBI and butanol extractable protein bound iodine, and decrease in T^3 uptake values; metyrapone test; pregnanediol determination.

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Editorials

Cervical Lymphography

THE DEVELOPMENT of a technique for visualizing cervical lymphatics via the use of radiopaque contrast agents is of great interest and reflects the increasing importance of this new radiographic device.* Unfortunately no one technique has so far been effective in visualizing the entire lymphatic system. Considerable experience has been accumulated in lymphangiography of the lower part of the body; but, while this technique is quite effective in visualizing the lymphatics up to the level of approximately L-2, it is ineffective in covering the area above this, including the upper periaortic areas and the mediastinum. There are other radiographic techniques which may be useful in outlining pathological adenopathy in the blind areas, such as inferior vena cavogram and intravenous pyelogram, but neither of these techniques has been as effective as lymphangiography. Consequently, any technique which increases the area susceptible to lymphangiographic study is of potential importance.

There are two general areas in which lymphangiography can be useful. The first is in the accurate staging of a known lymphoma, which appears to be of particular importance in the case of individuals with Hodgkin's disease. The evidence that high dosage radiotherapy is quite effective in treatment, particularly of patients with localized involvement, is now quite convincing. However, in the selection of patients for this mode of therapy, it is important to pinpoint all involved areas. In this determination, lymphangiography has been of particular importance since it exposes a considerable area of possible adenopathy hitherto concealed. If used in conjunction with inferior vena cavograms and intravenous pyelography, lymphangiography is particularly effective in delineating possible involvement of the abdomen. Lymphangiography also has the advantage that it can be used to follow patients, since contrast medium remains in the nodes for a considerable period of time, and these nodes can be re-examined by plain films of the abdomen. Thus, by the use of these techniques, patients with widespread disease who are not suitable candidates for intensive radiotherapy can be eliminated from such programs, and other patients who have unsuspected areas of involvement can receive radiotherapy directed to all the diseased areas.

There are certain disadvantages to lymphangiography, however, which should be noted. First of all, it is a time-consuming process which requires the patience and interest of the radiologist. In addition, there is a slight risk attached to the procedure. This risk appears most marked in individuals who have extensive pulmonary disease, and in such individuals lymphangiography probably should not be done. Despite this problem, however, a large series of patients have been studied at several centers for study of lymphoma, in-

*Sigel, Melvin E.: Cervical Lymphography. Minnesota Med 50:1035, 1967.

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cluding Stanford and Memorial Hospital in New York, and the technique has proved its utility in this broad experience.

Lymphangiography may also be of use in investigating a patient for an occult lymphoma. It is known that auto-immune hemolytic anemia may be the first manifestation of an underlying lymphosarcoma or Hodgkin's disease. Certain patients have been found who had no peripheral manifestations of lymphoma whatsoever and who had normal intravenous pyelograms. However, an abnormal lymphangiogram has been the first clue to the presence of an underlying lymphoma. Unfortunately, the technique has been of less value in the study of nonlymphomatous neoplasms.

For lymphangiography to be completely successful, however, it will first be necessary to make the procedure completely safe, relatively less time-consuming, and more effective in visualizing all the lymph node areas. If this can be accomplished, clinicians will have a tremendously powerful tool for the study of lymphoma.

F. Bruce Lewis, M.D.
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Mediastinoscopic Diagnosis of Sarcoidosis*

WITH CURRENT METHODS of management, precise diagnosis of intrathoracic conditions is of increasing importance. Intelligent utilization of knowledge of the lymphatic drainage of the lungs and mediastinum has afforded a simple and safe means for diagnosis of certain conditions which affect this lymphatic system.

Since Daniels[1] originally described biopsy of the scalene lymph nodes, various extensions have been proposed to increase diagnostic efficiency. Maloney and associates'[2] biopsy of the right thoracic duct lymph node has significantly increased the yield of positive cervical explorations; the disease can be diagnosed by this means in 80% of patients with nonpalpable nodes.

Only when cervical exploration fails to provide diagnostic material is further extension of nodal biopsy indicated. Such procedures as Harken and co-workers'[3] cervicomediastinal exploration and Carlens'[4] mediastinoscopy have made it possible to obtain diagnostic material which heretofore required more formidable surgical exploration. When biopsy material from either the neck or the mediastinum demonstrates noncaseating granuloma on pathologic examination, it is important to culture this material to be certain that specific organisms are not present. Only in this way is the diagnosis of sarcoidosis made more certain.

It has been stated that mediastinoscopy, or even thoracotomy, may be necessary to differentiate tuberculous hilar lymphadenopathy and certain other conditions from sarcoidosis.[5] In most instances, however, the correct diagnosis can be established without resort to these procedures. The true nature of the disease can usually be appreciated after careful review of the patient's clinical status and laboratory data, including the results of skin tests, x-ray examination of the chest, microbiologic studies, and biopsy of the scalene or thoracic duct lymph nodes.

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*Johnsen, A. F., Duvall, A. J., III, and Koop, S. H., Jr.: Mediastinoscopic Diagnosis of Sarcoidosis. Minnesota Med 51: 915, 1968.

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Infection in Hospitalized Patients

DRS. SALTER AND ZINNEMAN* in their comprehensive review of bacteremia and *Candida* septicemia draw attention to changes in medical practice that have altered the pattern of infection. There has been an increasing number of reports concerning infections associated with chemotherapy. Included among chemotherapeutic agents are antibiotics, steroids, and the various drugs used in the treatment of malignant disease. Infection is also noted with increasing frequency in association with other medical problems. An example is radiation therapy, which may be associated with an increased risk of infection. Also, the terminal event in leukemia, lymphoma, and metastatic malignancy is often related to infection. In addition, surgeons are implanting foreign substances in the form of prostheses with increasing frequency. Infections associated with foreign material are not easily controlled. Some patients are given drugs that alter their defense mechanism to aid in the acceptance of transplanted tissue. These individuals are more susceptible to infection, and when it occurs, treatment is usually very difficult.

There has also been a change in the type of organism encountered in that those with acquired or natural resistance to antibacterial drugs are more often associated with infection. Physicians are also finding more disease caused by organisms which were previously thought to be saprophytes. Some drugs such as steroids not only alter the immune mechanism of the body but also mask many of the signs and symptoms usually associated with infection.

The early recognition and proper antibacterial treatment of infections under these hazardous circumstances are imperative. The other side of the coin, of course, concerns prevention, and in this area there is much work to be done. Investigators are only now beginning to scratch the surface of more sophisticated means of protection for the individual and the hospital. Experiments are in progress in the use of plastic isolators, protective clothing, filters, laminar air flow, and various combinations of these protective barriers. Much of this work has been stimulated by the fact that it is now possible to maintain gnotobiotic or germ-free animals with only minimal difficulty. The outer-space program has also been helpful, since the need for dust-free, and in some instances germ-free, areas has led to rapid advances in construction of "clean rooms." Better sampling devices are also now available, which aid in the discovery of otherwise undetected microorganisms.

I am confident that in the foreseeable future far superior methods of isolation and protection of both patient and hospital will be available.

William E. Wellman, M.D.
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*Salter, W., and Zinneman, H. H.: Bacteremia and Candida Septicemia. Review of 185 Cases During A Four-Year Period. Minnesota Med. 50:1489, 1967.

Let the Tonsil Go with the Adenoid

IN THE JUNE 1967 ISSUE Dr. Donaldson presents a provocative report on that often discussed subject "The Tonsil and Adenoid Problem."* As in all branches of medicine, the pendulum swings from unbridled enthusiasm to ultra conservatism and then perhaps stabilizes itself in the mid-road between the extremes.

Dr. Donaldson outlines the present indications for tonsil or adenoid surgery and points out that the history of the patient's illness is vital in making this decision. Here the role of the referring physician as careful observer is

*Donaldson, James A.: The Tonsil and Adenoid Problem. Minnesota Med 50:933, 1967.

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W. H. J. Summerskill, M.D., Rochester, Minn.—*Gastroenterology*
Edward J. Kowalewski, M.D., Akron, Pa.—*General Practice*
John G. Masterson, M.D., Hines, Ill.—*Gynecology*
Ray W. Gifford, Jr., M.D., Cleveland, Ohio—*Internal Medicine*
Raymond V. Randall, M.D., Rochester, Minn.—*Internal Medicine*
William J. German, M.D., New Haven, Conn.—*Neurosurgery*
Robert A. Kinch, M.D., Montreal, Que.—*Obstetrics*
John R. Lynn, M.D., Dallas, Tex.—*Ophthalmology*
A. B. Sirbu, M.D., San Francisco, Calif.—*Orthopedic Surgery*
Douglas P. Bryce, M.D., Toronto, Ont.—*Otorhinolaryngology*
A. James French, M.D., Ann Arbor, Mich.—*Pathology*
Louis Gluck, M.D., Miami, Fla.—*Pediatrics*
Wilma C. Diner, M.D., Little Rock, Ark.—*Radiology*
James D. Hardy, M.D., Jackson, Miss.—*Surgery*
John W. Kirkland, M.D., Birmingham, Ala.—*Surgery*
Russell Scott, Jr., M.D., Houston, Tex.—*Urology*

Additional speaker to be announced.

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For information concerning the Assembly meeting write Secretary, The New Orleans Graduate Medical Assembly, Room 1538, 1430 Tulane Avenue, New Orleans, Louisiana 70112.

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most important. Donaldson's most controversial conclusion that adenoidectomy is often indicated without tonsillectomy will provoke disagreement. The temptation to remove the tonsils at the same time as the adenoids is great. While the child is under anesthesia one cannot always be certain that the tonsils are innocent. Further it may be unfair to expose the patient to a second surgical procedure. The fear of morbidity and postoperative complications from tonsillectomy should not be an important consideration in this day of excellent surgical management.

I believe that all doctors interested in the "tonsil and adenoid problem" should read and reread this excellent article, for it cannot but help in making for better management and understanding by those concerned.

Joseph L. Garten, M.D.
Minneapolis, Minnesota

Megaloblastic Anemia*

THE PAPER by Dr. Yutani and his associates* on gastrointestinal causes of megaloblastic anemia illustrates why so much of the outstanding work on the megaloblastic anemias has been carried out by workers in the field of gastroenterology. With few exceptions, an abnormality or an abnormal function in the gastrointestinal system is of primary etiologic importance in this type of anemia.

These authors discuss the findings of many workers who have studied auto-immune mechanisms involving parietal cell and intrinsic factor antibodies in addisonian pernicious anemia. Another study along this line, which has been of considerable interest, is that of Ardeman and Chanarin[1] who, along with a number of others interested in this disease, have studied the effect of adrenal corticosteroids on vitamin-B_{12} absorption in patients with pernicious anemia. In one investigation they observed 11 patients with vitamin-B_{12} deficiency. Eight of them had addisonian pernicious anemia, and five of these had intrinsic factor antibodies in their serum. Two had undergone partial gastrectomy for duodenal ulcer, and one had undergone total gastrectomy for carcinoma seven years previously.

These investigators observed that therapy with prednisone, usually 40 mg daily for three to five weeks, resulted in an improvement in vitamin-B_{12} absorption in seven of the eight patients with addisonian pernicious anemia. It was equally effective in patients with or without demonstrable intrinsic factor antibodies. They also noted that improvement in absorption of vitamin B_{12} preceded any decline in the titer of intrinsic factor antibodies. It was also recorded that, in this group of five patients with intrinsic factor antibodies in the serum, three had an increase in the amount of intrinsic factor produced; but in two there was little change.

Ardeman and Chanarin pointed out that the efficacy of steroids in improving vitamin-B_{12} absorption in almost all patients with pernicious anemia suggested that there may not be any real difference between those patients with and those without demonstrable serum antibodies. It was of interest, however, that they failed to elicit a response in the patients who had megaloblastic anemia after subtotal gastric resection. The lack of response suggested to the authors that the pathogenesis of the gastric atrophy in pernicious anemia might be different from the atrophy appearing in the gastric remnant after partial gastrectomy. This difference could be explained by the concept that in pernicious anemia the atrophy may be largely the consequence of an auto-immune mechanism, while after partial gastrectomy, it may be that ischemic factors are more important. The improvement in vitamin-B_{12} absorption before any change in titer of the intrinsic factor antibody in the blood suggested that these antibodies were of little significance, and it was proposed that the important antibodies were those in such tissues as the gastric mucosa and epithelial cells lining the villi in the ileum where they came in contact with the antigen.

Complexities in the pathogenesis of megaloblastic anemias continue to be demonstrated by a number of investigators, and pernicious anemia is no exception.

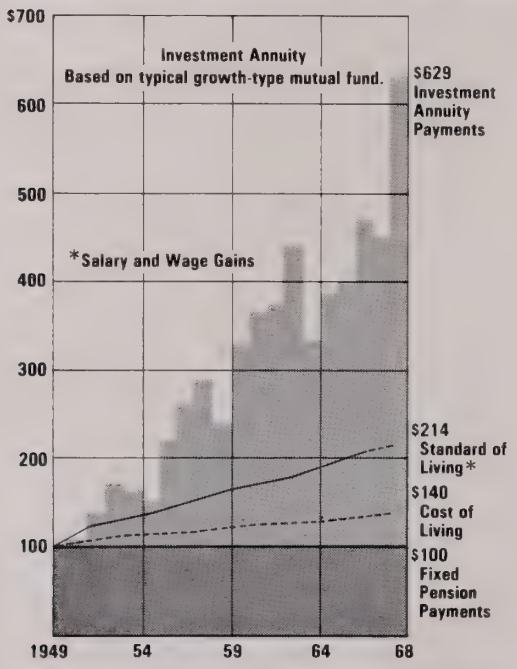
D. C. Campbell, M.D.
Rochester, Minnesota

*Yutani, F. M., Farmer, R. G., and Hoffman, G. C.: Gastrointestinal Causes of Megaloblastic Anemia. Minnesota Med 51:1123, 1968.
Reference can be secured from the author.

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Intravenous Regional Anesthesia*

RECENT MEDICAL literature frequently contains articles on the ease of performing regional intravenous anesthesia. This technique undoubtedly has wide application but, because of the apparent ease of achieving anesthesia, persons who are relatively inexperienced may well attempt to use it when adequate supportive facilities are not available. "Adequate supportive facilities" means necessary medication and equipment to combat complications that may result from the use of local anesthetic agents.

Before using the local anesthetic agents required for this technique, one should be thoroughly familiar with the proper handling of complications that may follow. If respiratory arrest should occur, the means and ability to assure the patient of an adequate airway should be available. Medication for stopping convulsions should always be at hand, and the person administering the anesthetic should know how to use such medication. If cardiovascular collapse should develop, one should be able to support the circulation adequately at a moment's notice. All in all, one should be prepared to cope with all eventualities.

I would like to stress that this technique is not to be used indiscriminately in a busy office practice just because it is easily performed. It is fraught with the usual dangers associated with anesthesia. Remember, there is no minor anesthetic procedure.

Charles J. Restall, M.D.
Rochester, Minnesota

*Wier, G. T.: Intravenous Regional Anesthesia: A New Technique. Minnesota Med 51:771, 1968.

Weakness and Chronic Heart Failure

IT HAS BECOME increasingly apparent in recent years that amyloidosis may present with a variety of clinical manifestations which could mimic a number of other clinical entities. In the case of amyloidosis of the heart presented by Lovshin,* it was necessary to pursue diagnostically several alternative possibilities, including mitral stenosis, left atrial tumor, thromboembolic pulmonary vascular disease, and constrictive pericarditis. This seems reasonable because cardiac problems of apparent obscure cause are often shown to be uncommon forms of common heart disease and as such may be amenable to cure or successful therapy. This is particularly important in a case of progressive and refractory congestive heart failure in which there is clinical or laboratory evidence suggestive of constrictive heart disease. In this instance, exploration of the pericardium is necessary to determine whether or not constrictive pericarditis is present.

The establishment of the diagnosis of cardiac amyloidosis is frustrating therapeutically, but, with a better understanding of the amyloid process, one can hope that successful medical therapy may become available in the future. Until then, it is conceivable that some patients refractory to all available forms of medical therapy may become amenable to the dramatic forms of surgical therapy currently under development.

John Merideth, M.D.
Rochester, Minnesota

*Lovshin, L. L.: Weakness and Chronic Heart Failure. Minnesota Med 51:1105, 1968.

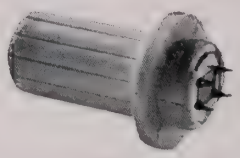
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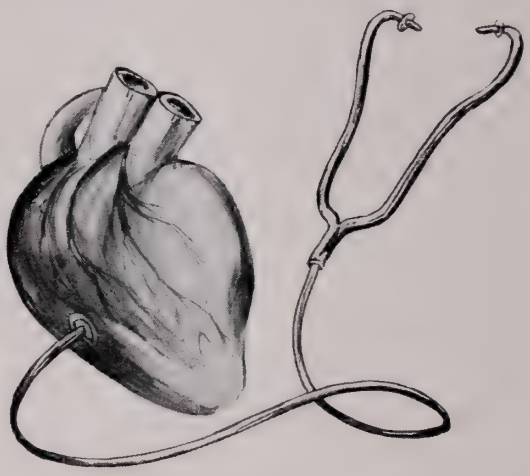




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In 1945 there was a situation analogous to the one we are now facing. May I quote from Pastor Martin Niemoller? "In Germany the Nazis came for the Communists and I didn't speak up because I was not a Communist. Then they came for the Jews and I did not speak up because I was not a Jew. Then they came for the Trade Unionists and I did not speak up because I was not a Trade Unionist. Then they came for the Catholics and I was a Protestant, so I did not speak up. Then they came for me. By that time there was no one to speak up for anyone." Unquote!

Stephan H. Earl, M.D.
Minneapolis, Minnesota

Test Your Word Score

Colporrhaphy—*operation of suturing the vagina* (page 1705).

Metrorrhagia—*abnormal uterine bleeding* (page 1705).

Ancylostomiasis—*a variety of hookworm disease* (page 1713).

Giardiasis—*an intestinal infection due to Giardia, a protozoan organism* (page 1713).

Verrucous—*wart-like* (page 1719).

Xanthelasma—*a form of xanthoma, affecting the eyelids with soft, yellowish spots* (page 1721).

Dysgerminoma—*solid ovarian or testicular tumor derived from germinal spithelium that is undifferentiated sexually* (page 1726).

Diathesis—*the constitutional state disposing to a disease* (page 1731).

Chromophobe—*a not easily-stained cell* (page 1733).

Lupus—*Latin for wolf* (page 1780).

In-vitro—*within a glass; observable in a test tube* (page 1785).

Telangiectasia—*dilatation of small vessels* (page 1805).

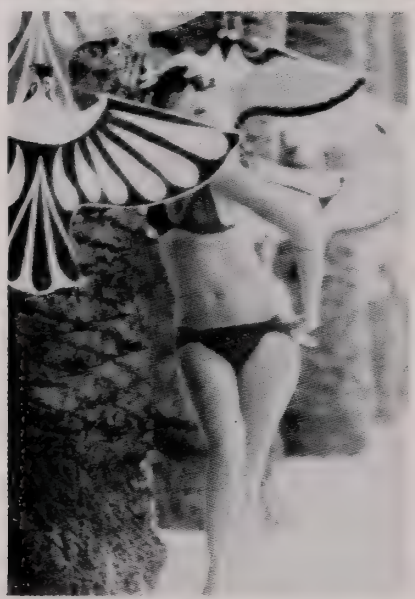
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The Editor's Soliloquy

Manuscripts

Some people love to write and most people love to read. The editor loves both; but there can be a limit. A manuscript in the following vein, though informative and objective, can be appallingly tedious and inconsequential:

Title

"An Evaluation of Headache as It Pertains to Males and Females in Kandiyohi County During Hunting Season From October 1 to January 1.

With Special Emphasis on Posterior Occipital Headache

A Report on My Double-Blind Series of Five Consecutive and Unselected Cases.

Introduction

"This manuscript is written for the purpose of informing interested readers about headache as it occurs in Kandiyohi County . . . etc.

"The literature on the subject has been carefully examined and exhaustively reviewed, resulting in the finding that of 350 authorities listed in the References, 174 are cognizant and 176 unaware of the problems and complications involved. The author has personally and critically perused all of these references except the last 345, for the authenticity and perspicacity of which he accepts the word of Longtalk, Jabber and Longwinded, whose erudite resume was published in the Annals of 1946. (To antedate 1946 would seem unnecessary.)

"I now propose adding my own supplementary series.

Body of Manuscript

"In my professional experience with headaches, summed up in my series of five (four males and one female), 60% (3 cases) showed favorable and 40% (2 cases) unfavorable results, which seems to substantiate overwhelmingly the findings of Stretch and Strain and coworkers, who found favorable results in 51.58%. True, their series is somewhat larger; but the validity of any study lies not so much in its size as in the thoroughness and accuracy with which it is conducted. (Incidentally, I am omitting statistics on age and sex ratios as not significantly pertinent or contributory.) On the basis of my educated guess, therefore, I believe I am justified in making a reliable assumption in the affirmative—viz., a corroboration of the previous deductions already so conscientiously and laboriously arrived at by my distinguished predecessors in the field.

Comments

"With the numerous investigations of Knowitall et al. of Pepp State and the qualifying but nonetheless confirmatory analyses of Doubtful and Dubious of Modalities Institute on the Hudson, added to my own, it appears that headaches can be assured with the probability of error of only 1.5 to the nth squared power over 3.

Conclusion

"With this verified and therefore cogent figure I conclude my expatiation. I have cited the literature; I have added statistics based on my own five cases; and I have thereby concurred in a valuable if not momentous conclusion."

Editor's Note: An addendum of two more cases reached my desk subsequent to the presentation of this article for publication 4:32 p.m., October 1, 1955 (establishing priority) but I have chosen to exclude them from the series on the basis that no additional value would accrue from their inclusion.

Carl O. Rice, M.D.

Old Doc Hess says: From the spoken word to the readable manuscript there's been a lot of boiling and re-boiling.

There is a time to wink as well as to see.—Thomas Fuller



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Warning: If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Instances of severe bleeding have occurred. Persistent or severe dyspepsia may indicate peptic ulcer; perform upper gastrointestinal x-ray diagnostic tests if drug is continued. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy. Use with caution in the first trimester of pregnancy and in patients with thyroid disease.

Precautions: Before prescribing, carefully select patients, avoiding those responsive to routine measures as well as contraindicated patients. Obtain a detailed history and a complete physical and laboratory examination, including a blood count. Patients should not exceed recommended dosage, should be closely supervised and should be warned to discontinue the drug and report immediately if fever, sore throat, or mouth lesions (symptoms of blood dyscrasia); sudden weight gain (water retention); skin reactions; black or tarry stools or other evidence of intestinal hemorrhage occur. Make complete blood counts at weekly intervals during early therapy and at 2-week intervals thereafter. Discontinue the drug immediately and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.

Adverse Reactions: The more common are nausea and edema. Swelling of the ankles or face may be minimized by withholding dietary salt, reduction in dosage or use of diuretics. In elderly patients and in those with hypertension the drug should be discontinued with the appearance of edema. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. The patient should be instructed to take doses immediately before or after meals or with milk to minimize gastric upset. Drug rash occasionally occurs. If it does, promptly discontinue the drug. Agranulocytosis, exfoliative dermatitis, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), or a generalized allergic reaction similar to serum sickness may occur and require permanent withdrawal of medication. Agranulocytosis can occur suddenly in spite of regular, repeated normal white counts. Stomatitis, salivary gland enlargement, vomiting, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported. While not definitely attributable to the drug, a causal relationship cannot be excluded. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, hypersensitivity angiitis, pericarditis and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.



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Warning: In renal impairment, since liver toxicity is possible, lower doses are indicated; during prolonged therapy consider serum level determinations. Photodynamic reaction to sunlight may occur in hypersensitive persons. Photosensitive individuals should avoid exposure; discontinue treatment if skin discomfort occurs.

Precautions: Drowsiness, anorexia, slight gastric distress can occur. In excessive drowsiness, consider longer dosage intervals. Persons on full dosage should not operate vehicles. Nonsusceptible organisms may overgrow; treat superinfection appropriately. Treat beta-hemolytic streptococcal infections at least 10 days to help prevent rheumatic fever or acute glomerulonephritis. Tetracycline may form a stable calcium complex in bone-forming tissue and may cause dental staining during tooth development (last half of pregnancy, neonatal period, infancy, early childhood).

Adverse Reactions: *Gastrointestinal*—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. *Skin*—maculopapular and erythematous rashes; exfoliative dermatitis; photosensitivity; onycholysis, nail discoloration. *Kidney*—dose-related rise in BUN. *Hypersensitivity* reactions—urticaria, angioneurotic edema, anaphylaxis. *Intracranial*—bulging fontanels in young infants. *Teeth*—yellow-brown staining; enamel hypoplasia. *Blood*—anemia, thrombocytopenic purpura, neutropenia, eosinophilia. *Liver*—cholestasis at high dosage.

Upon adverse reaction, stop medication and treat appropriately.

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ANSWER: The plasma phenolsulfonphthalein index test is based on serial determinations of plasma phenolsulfonphthalein plasma levels following the intravenous injection of a single dose of the dye. The index is determined by calculating the rate of decrease of the plasma phenolsulfonphthalein values over a given time period (usually 15-35 minutes) following the injection. Rate of fall of the plasma phenolsulfonphthalein plasma values are directly related to renal function.

The phenolsulfonphthalein index test overcomes several problems encountered in the standard plasma phenolsulfonphthalein test, such as those arising in cases of bilirubinuria, hematuria, urinary retention in the upper or lower urinary tract, and where difficulties are met in collection of urine specimens (poor patient cooperation, fistulas, etc.).

Harold D. Kletschka, M.D.
Houston, Texas

LUPUS ERYTHEMATOSUS

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ANSWER: Lupus erythematosus cell formation is thought to be due to an antibody to nucleoprotein. Lupus erythematosus cells are observed in systemic lupus erythematosus (about 75% of such cases), rheumatoid arthritis (about 10%), scleroderma (10%), and lupoid hepatitis. Although they have been recorded as occurring in association with certain drug reactions it is believed that most such cases on close investigation will be found to have an underlying lupus diathesis. It is futile to attempt correlation of positive lupus erythematosus cell test results with the clinical picture or as a guide to treatment. The Hyland "Lupus Erythematosus Test" results are positive in only about one third of patients with lupus erythematosus cells but is almost specific in detecting activity of systemic lupus erythematosus.

Harold D. Kletschka, M.D.
Houston, Texas

Every man who takes office in Washington either grows or swells.—Woodrow Wilson

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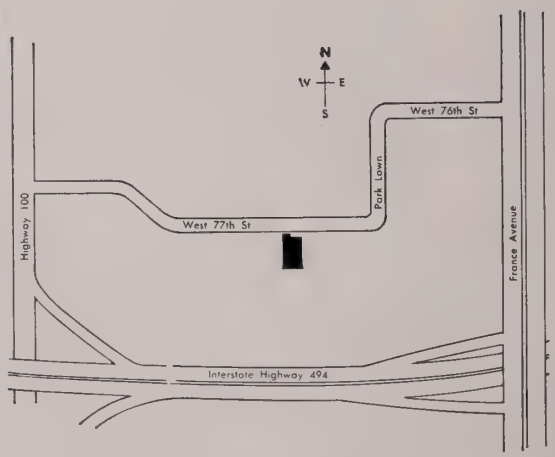
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Routine Chest Film

ON HER FIRST hospital admission this 60-year-old white female was referred for evaluation of a routine chest film. A similar routine chest film done one year before had been read as normal.

This lady, on admission, revealed no respiratory symptoms except for a cold some two weeks previously. There was no chest pain, hemoptysis, dyspnea, or association with persons having tuberculosis, but since her cold, an intermittent non-productive cough had persisted. On direct questioning she admitted to progressive hoarseness over the previous 24 hours prior to admission. She had smoked one and one-half packs of cigarettes a day for the preceding 30 years, but had quit about two years before because of a mild non-productive morning cough.

Physical examination of the chest showed decreased breath sounds and fremitus in the left upper lobe, with some increased, coarse breath sounds in the left lower lobe. There were no rales or rhonchi. Indirect laryngoscopy revealed the left vocal cord to be paralyzed. Three days after admission the patient was noted to be markedly dyspneic with expiratory stridor.

The admission chest roentgenogram disclosed a large anterior mediastinal mass and atelectasis of the left upper lobe (Figures 1-a and 1-b).

What is your diagnosis? (See next page).

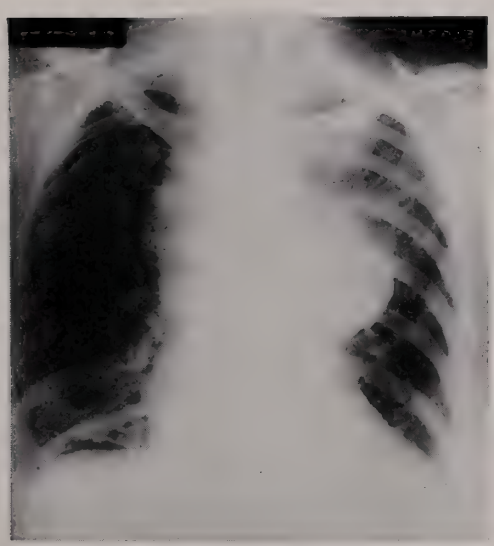


Figure 1-a.

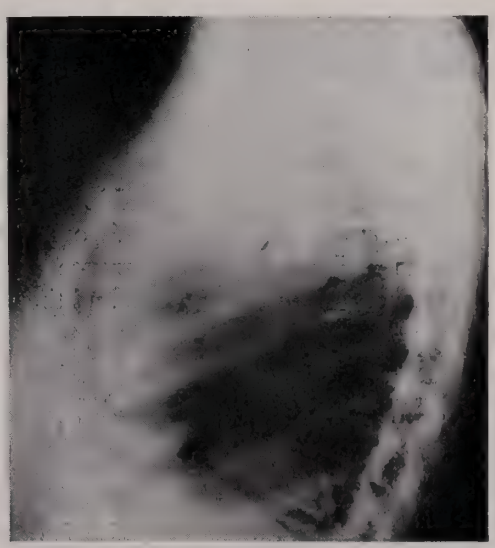


Figure 1-b.

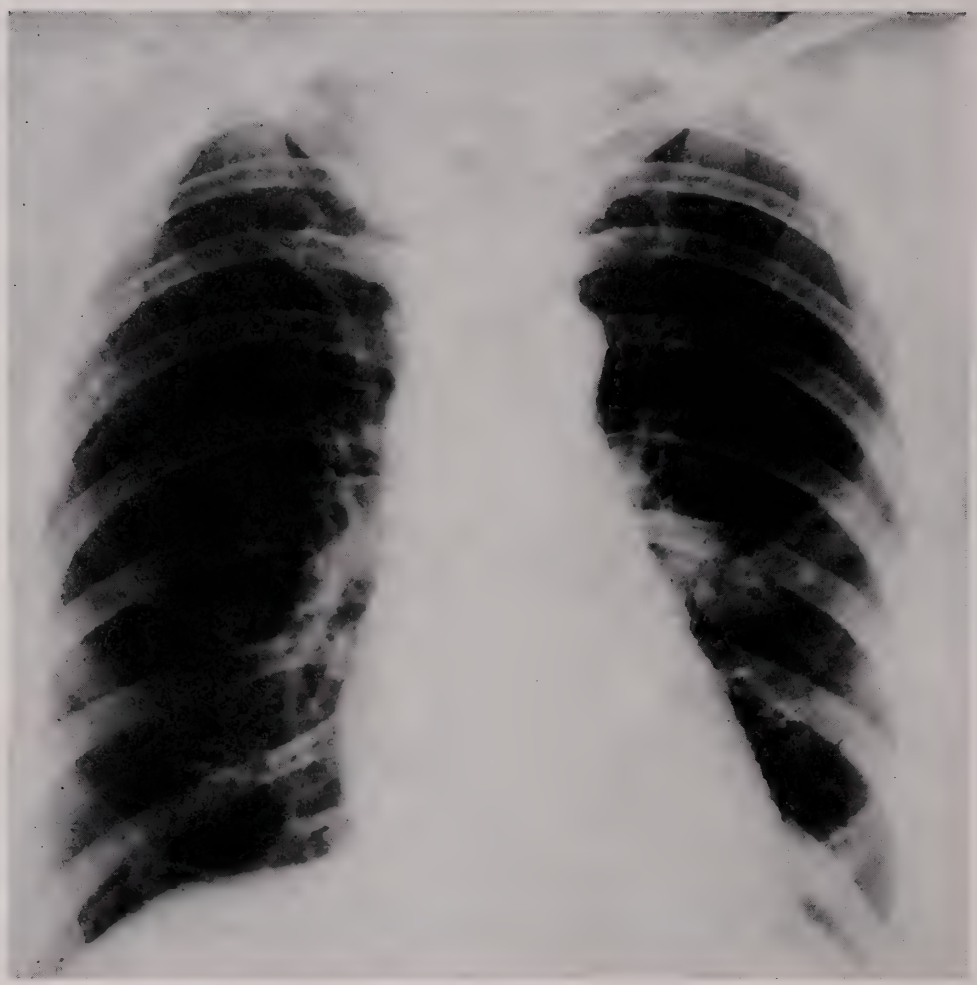


Figure 2.

Diagnosis: Poorly differentiated small cell carcinoma, with secondary atelectasis of the left upper lobe.

The differential diagnosis consistent with a rapidly expanding anterior mediastinal mass would be between that of lymphoma, carcinoma, or aneurysm. Sarcoid would be unlikely in so anterior a site as this (Figures 1-a and 1-b). The physician should consider carcinoma more likely when associated atelectasis of an entire lobe is present. This lady was given 10 treatments of cobalt 60 teletherapy with 2500 r to the mediastinum. Immediate symptomatic improvement was noted, and some two months later only residual fibrosis remains (Figure 2). Recurrence of the tumor and/or distinct metastases, however, are to be expected, and the prognosis remains grave.

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Buttocks

We all have something to fall back on, and I never knew a phony who didn't land on it eventually.—Wilson Mizner



Fracture Conference

Problem Fractures in Children

The Elbow

Dr. Hamlet A. Peterson:*

We would like to present three challenging and interesting cases. Also, Dr. Goodwin has prepared a short review of the pertinent literature on one of the problems covered.

Report of Cases

Case 1

Dr. Richard C. Sweeting:†

The first case is that of a five-year-old girl who fell off her bicycle in June 1967. The physician in her home community found a simple oblique fracture of the middle third of the right ulna. Her arm was placed in a long arm cast, and the usual instructions and precautions were given. She was first seen at our clinic five weeks after the fracture, with her arm still in the cast.

Dr. Peterson:

According to the referring letter, there was a simple fracture of the ulna. Upon arrival the cast was removed, and roentgenograms were taken (Figure 1 A and B). Dr. Mess, how do you think the fracture is coming along?

Dr. C. F. Mess:‡

It looks as if there is no evidence of union now after five weeks. I would like to see some signs of bony union. There is still a fracture line between the segments.

Dr. Peterson:

At five weeks would you put her arm back in a cast?

---

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Conference held at the Mayo Clinic, Rochester, on April 1, 1968.

Dr. R. H. Turner:*

I probably would put her arm in a cast for another two or three weeks and see what it looked like at that time.

Dr. Peterson:

Her arm wasn't put in a cast. She was advised to begin motion.

Dr. Sweeting:

Five weeks later she returned; examination showed full extension but incomplete flexion. These roentgenograms were taken (Figure 1 C).

Dr. Peterson:

Now what do you think, Dr. Mess?

Dr. Mess:

There is a dislocation of the radial head.

Dr. Peterson:

In the history, emphasis was placed on the ulna, wasn't it? The patient's physician evidently missed detecting the dislocation of the radial head. It was also missed when she was first seen at our clinic (Figure 1 B). Ten weeks have elapsed since the fracture. Except for some loss of complete flexion the elbow has good motion, and the patient has no complaints. There is a rather obvious prominence over the lateral side of the elbow.

Dr. R. N. Stauffer:†

I think something needs to be done. It looks as if the ulna has shortened. How much pronation and supination did she have?

Dr. Peterson:

There was normal supination and pronation. After what duration would it become hazardous to reduce a dislocated radial head?

Dr. D. E. Fisher:‡

I think Dr. Pages' Instructional Course traced this problem. He believed that reduction ought to be attempted because the growth stimulation of the pressure on the end of the bone is lacking since there is no contact with the humerus. Also, the deformity will continue if reduction is not done.

Dr. Peterson:

If it was six months or one year later, would you do anything? There must be some sort of time limit. The girl is young.

Dr. Fisher:

I think that the girl will still have the basic problem no matter what the time limit is.

Dr. Peterson:

Even if the dislocation occurred one, two, or five years previously? Dr. Blount[1] has stated that after three months a dislocated radial head should not be reduced. There is usually full supination, diminished flexion, and an obvious deformity. Dr. Lipscomb, would you agree with leaving it unreduced after three months, but attempting reduction prior to this three-month limit?

---

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Dr. Paul R. Lipscomb:*

Dr. F. H. Stellings has reported a series of cases a few years ago and reported them again at the Academy Meeting after a long-term follow-up. The patients who had been left alone did far better and had better elbows as adults than those who had a late reduction of the radial head dislocation. This is at 10 weeks and right on the borderline. Certainly you are not going to find normal anatomic relationship, and some anatomic elements will be obliterated.

Dr. Peterson:

I researched the literature and found the three-months' figure to be gen-

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Fig. 1—(Case 1). (*A*) and (*B*) Right forearm five weeks after injury. (*C*) Right forearm 10 weeks after injury. (*D*) Reduction of proximal portion of right radius was held with a Kirschner wire for three weeks. (*E*) Final result nine months after injury.

erally accepted. This research resulted in a two-week delay, but 12 weeks after injury the child underwent surgery. Dr. Sweeting, tell us what followed.

Dr. Sweeting:

With the child under general anesthesia, another attempt was made at closed reduction. This was unsuccessful. After an easy and uneventful open reduction, the annular ligament was reconstructed. The radial head was held in the reduced position by a Kirschner wire, as shown on the roentgenogram (Figure 1 D).

Dr. Peterson:

Three weeks later the wire was removed and the arm again put back into a long-arm cast. Six weeks after operation and four months after the fracture, the final cast was removed. A sling was worn for three weeks. The girl has done very well since then. Nine months after fracture (Figure 1 E) the range of motion was normal. So this case turned out well, and all concerned were happy. I am sure there is a time limit after which this type of injury should be left alone. Exactly what it is might depend somewhat on the age of the patient. This child was only five years old. I don't think the ulna was shortened, because the radial head was very easily reduced at surgery. Had the ulna been shortened, this would not have been so easy; then there would have been a question of how much force to apply. One would not want to traumatize the elbow or compress the epiphyseal plate in so doing.

Dr. Lipscomb:

Did you reconstruct the orbicular ligament?

Dr. Peterson:

Yes, a good portion was present, and it was sutured.

Dr. J. R. Sebald:*

How did you explain to the patient's parents the lack of treatment of the radial head dislocation initially?

Dr. Peterson:

They did not question it, and it wasn't brought up.

Dr. Sebald:

Did you tell them that the fracture had not united properly?

Dr. Peterson:

No. I think it was stated that the roentgenograms at 10 weeks showed a dislocation, and this was as far as the discussion went. Some patients' parents are more inquisitive than others.

Dr. Mess:

What would be the functional result of premature closure of the proximal radial epiphysis in a child of this age?

Dr. Peterson:

It would be similar to the situation resulting from removal of the radial head and would be rather drastic. Continued ulna growth would produce radial deviation of the hand and would limit forearm rotation.

Case 2

Dr. Sweeting:

The next case is that of an eight-year-old boy who fell off a slide. He

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landed on his outstretched left arm and immediately had pain in his left elbow. There was slight swelling in the antecubital fossa on the left side and tenderness over both condyles, with a good radial pulse. Roentgenograms were taken (Figure 2A and B).

Dr. J. H. Shertzer:*

On the lateral view, the ulna is overriding the distal portion of the humerus.

Dr. Peterson:

You say on the lateral view? Do you think that's normal?

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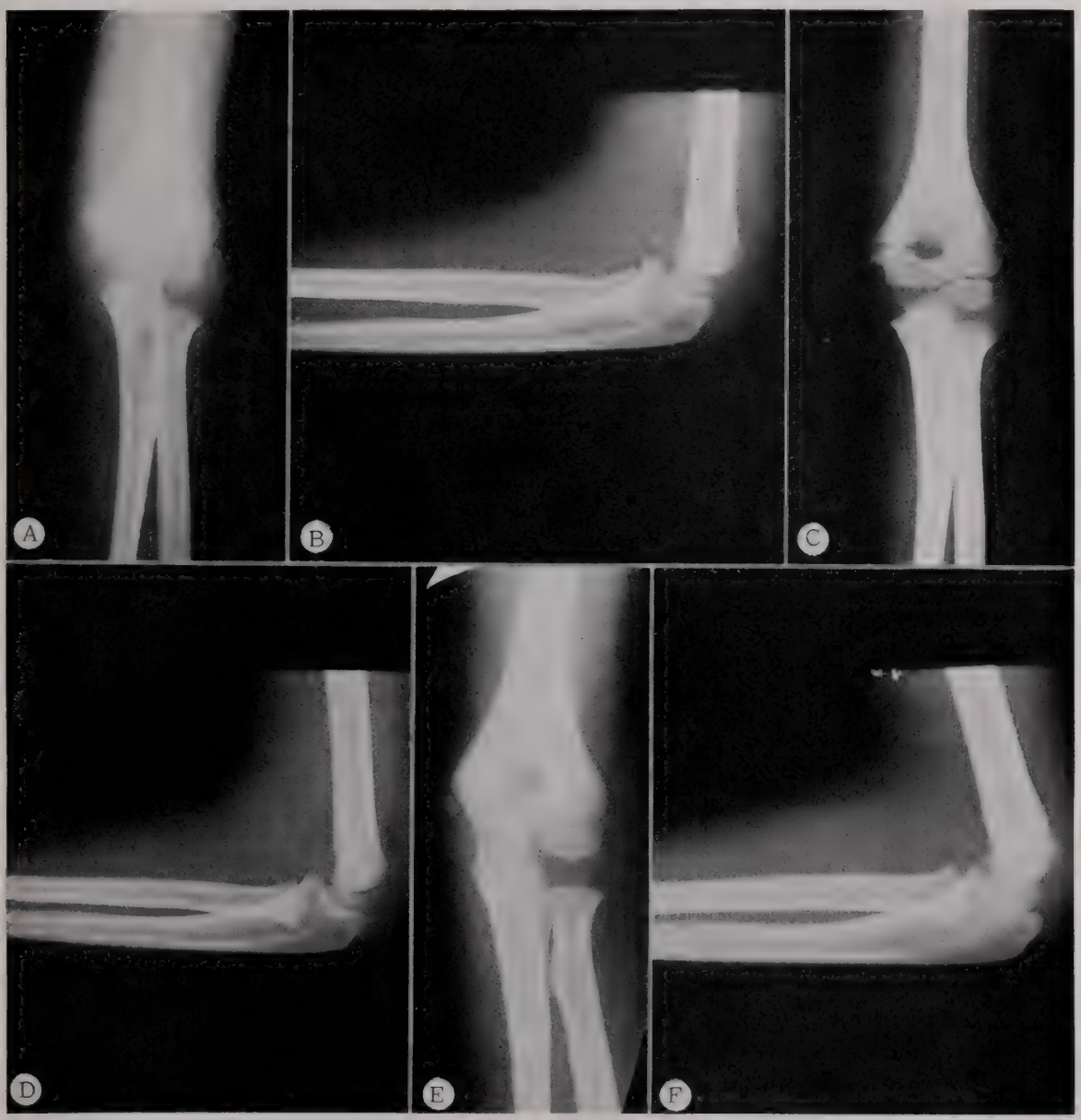


Fig. 2—(Case 2). (*A*) and (*B*) Lateral view of left elbow shows positive fat-pad sign. (*C*) and (*D*) In addition to the positive fat-pad sign, the anteroposterior view also shows a transcondylar fracture. (*E*) and (*F*) Ten weeks after injury, fat-pad sign is no longer present and the fracture is healing.

Dr. Shertzer:

It could be, now that I look at the anteroposterior views.

Dr. Peterson:

Films were interpreted by the radiologist as showing no abnormality.

Dr. S. Goldman:*

It looks as if there is a positive fat-pad sign.

Dr. Peterson:

What is a "fat-pad sign"?

Dr. Goldman:

Increased pressure within the elbow joint in a child causes some dislocation of the normal fat about the elbow. When this occurs, there is a radiolucent change in most of the tissues about the distal end of the humerus.

Dr. Peterson:

What do you think of the radiolucent area on a posterior aspect of the humerus? What does it indicate?

Dr. Goldman:

It usually indicates some intra-articular fracture.

Dr. Peterson:

Must it always be a fracture?

Dr. Goldman:

No, but there is always trauma around the elbow, with increased joint pressure.

Dr. Peterson:

Increased fluid in the elbow could be produced by a fracture. But a fracture was not seen on the roentgenogram. What would you do with this child?

Dr. Goldman:

I would put his arm in a large padded dressing and take more roentgenograms in a few days.

Dr. Peterson:

Do you think these roentgenograms are adequate? Additional roentgenograms seem necessary. Comparison roentgenograms of the opposite elbow looked identical, except for the absence of a fat-pad sign. Therefore, roentgenograms were taken again the same day. The new ones (Figure 2C and D) showed a fracture through the distal portion of the humerus: a transcondylar type of fracture. The child was immobilized. How long should the fat-pad sign remain positive?

Dr. Sweeting:

The cast was removed in three weeks and a sling applied.

Dr. Peterson:

Roentgenograms at six weeks (Figure 2 E and F) showed the fracture to be healing and the fat-pad sign to be absent. The patient did well.

Case 3

Dr. Sweeting:

Next is the case of a 14-year-old boy who slipped and fell on the sidewalk directly onto his flexed left elbow, striking the olecranon. Immedi-

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Fig. 3—(Case 3). (*A*) and (*B*) Left-elbow intercondylar fracture and positive fat-pad sign. (*C*) and (*D*) Four months after injury, the fat pad has a normal appearance and the fracture has healed.

Note: For the reader's benefit, Figure 3 C and D is shown of the patient four months after injury. The fracture has healed; the fat-pad sign is no longer present.

ately he had pain and swelling at the site of injury. Roentgenograms were taken (Figure 3A and B).

Dr. Peterson:

Here again, on the lateral view, there is a positive fat-pad sign. Note the elevated "moon-shaped" area of radiolucency anteriorly. Normally, there should be a triangular area of radiolucency along the anterior portion of the humerus into the coronary fossa. There is also a fat-pad sign on the posterior aspect, which represents bulging or posterior displacement of the triceps tendon. Let's stop here and have Dr. Goodwin tell us about the fat-pad sign.

Fat-Pad Sign

Dr. H. N. Goodwin:*

The capsule of the elbow joint encloses the articular structures of the joint and is composed of a synovial and a fibrous layer. Between the fibrous and the synovial membranes there are three main collections of fat, the largest pad in the posterior region of the olecranon fossa. This pad is pressed into the fossa by the triceps mechanism during flexion. The other two pads are situated anteriorly in the coronoid and radial fossae into which they are pressed by the brachialis during extension. Bledsoe and Izenstark[2] demonstrated fat-pad displacement by injecting fluid into the elbow joint of cadavers. A true lateral projection of the elbow flexed to 90° is the optimal view for demonstrating fat-pad displacement. Because of the difference in x-ray absorption of fat, muscle, and bone, the fat is more readily visible on the roentgenogram.

In normal elbows, the anterior fat pads are visualized as a single triangular radiolucent area. Griffing[3] believes that the anterior fat-pad sign is of little value in the diagnosis of a traumatic lesion and is of academic interest only. The posterior fat pad is usually not visible on lateral flexion views of the normal elbow because the pad lies deep in the olecranon fossa and is overshadowed by bone. When displaced, this pad is seen as a radiolucent area above the olecranon fossa, posterior to the humerus. Often the interior border is concave, due to extrinsic pressure of the joint fluid. The demonstration of fat-pad displacement is suggestive of injury or disease about the elbow joint, including joint effusion secondary to arthritis and trauma.

Nelson[4] suggested that the posterior fat-pad sign is seen only in cases of trauma; he has stated that he has never seen fat-pad displacement caused by serous or purulent joint effusion. Norell,[5] however, reported seeing this sign in various types of arthritis of the elbow joint. If the joint capsule is ruptured, the escape of fluid prevents displacement of the fat pad. Also, if a fracture does not communicate with the synovial cavity, the pad may not be displaced. The posterior fat-pad sign has its greatest diagnostic use in obscure fractures about the elbow joint, especially those of the radial head. In closing, it can be said that evidence of fat-pad displacement, seen on the lateral roentgenographic view of the elbow, usually indicates pathologic change in the elbow.

Dr. Peterson:

In the literature there were only four references to this sign.[2-5] The important thing to remember is that two prerequisites are necessary: (1) an

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intact capsule and (2) increased fluid within the joint that pushes the fat proximally. If the fat-pad displacement is seen, a search for a fracture should be made; however, other possible causes should be kept in mind.

Dr. L. F. A. Peterson:*

How long does the fat-pad sign remain positive after injury?

Dr. H. A. Peterson:

One article reported two to three weeks and another two to four days. Naturally, the length of time would depend on how fast the increased fluid in the joint could be absorbed.

Dr. M. B. Coventry:†

Our residents must remember the order of relative radiologic densities, because these are the basis of the fat-pad sign.

Dr. H. A. Peterson:

Thank you, Dr. Coventry. The order of relative density is fat, muscle, fluid, and bone.

Our time is nearly up; we must adjourn. These cases illustrate three salient points. First: In the event of a fracture of the midshaft of the ulna, one should always look for an associated dislocation of the same radial head. When this occurs, it is referred to as a Monteggia fracture, and treatment must be directed not only at the reduction of the fracture but also at the replacement of the dislocated head. Second: If the dislocation of the radial head is recognized late, as in our first case, an attempt at open reduction is justified up to three months after the injury. Third: The presence of the positive fat-pad sign should indicate to the practitioner that pathologic change exists in the elbow joint or the distal portion of the humerus.

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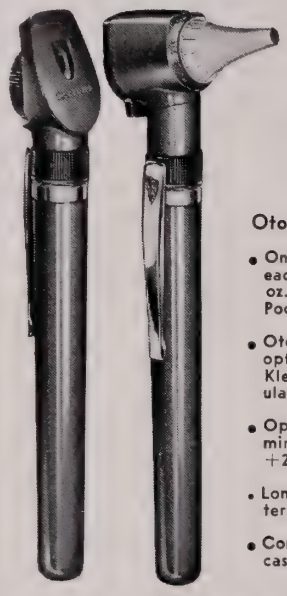
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In our country we have those three unspeakably precious things: freedom of speech, freedom of conscience, and the prudence never to practice either.—Mark Twain

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Folks that blurt out just what they think wouldn't be so bad if they thought.—Frank Hubbard



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Dermatology

Rosacea

ROSACEA (ACNE ROSACEA) is a common skin disease which affects the face. It may cause considerable embarrassment to the affected individual, for the layman often associates rosacea with gluttony and the excessive consumption of alcohol. The disease may occur in either men or women and is rare before the third decade.

Symptoms

Rosacea appears exclusively on the face and is most pronounced on the so-called flush areas (cheeks, nose, center forehead). Various stages may be recognized but are by no means distinct or exclusive from each other. The erythematous stage is characterized by flushing of the cheeks, nose, forehead and chin. The erythema is usually transient at first, lasting only a few hours. It may be induced by cold, heat, alcohol, spicy foods, coffee, etc. Nervous tension may also be associated with the flushing. Within varying periods of time telangiectasia of the superficial blood vessels occurs, resulting in a permanent erythema in the affected areas.

As a rule, there is an associated seborrhea involving the face and/or scalp, while the orifices of the sebaceous glands become prominent. The process may progress no further; however, in some individuals superficial or deep papules

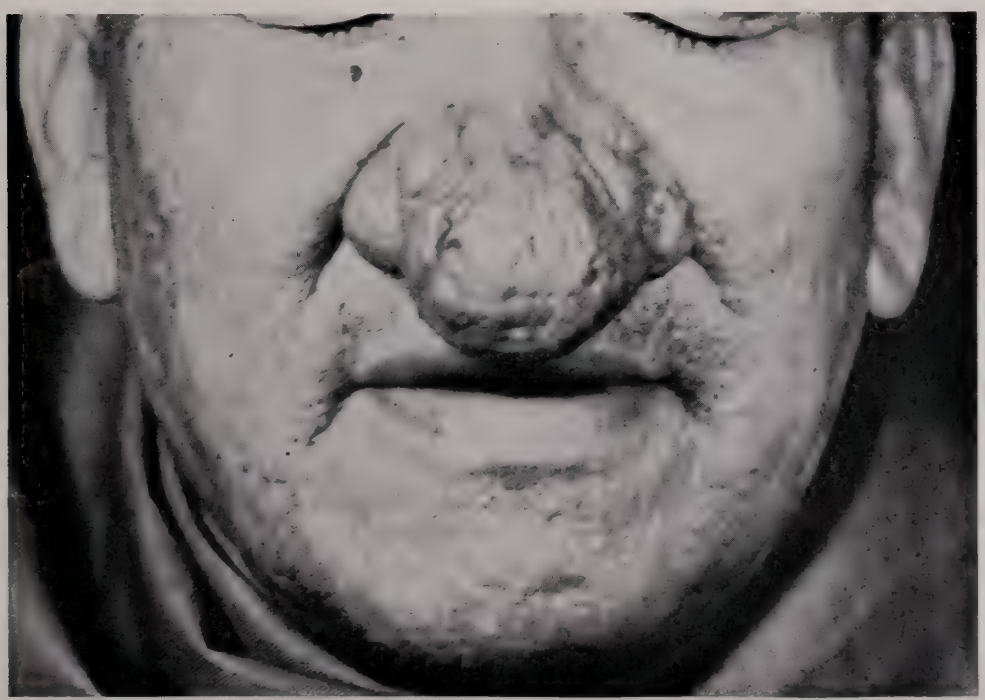


Figure.

and pustules occur. Such lesions resemble those of acne vulgaris, although the underlying erythema and the distribution, as well as age, help to differentiate the two conditions. In some cases the disease continues and deep cystic nodules and pustules develop. The lesions may even become abscesses with discharging sinuses. Scarring similar to that of acne vulgaris may occur.

A marked increase in size of the sebaceous glands can lead to progressive hypertrophy and lobulation of the nose called rhinophyma (Figure). The glandular orifices become conspicuous and an oily seborrhea is present. This latter stage is most common in men and rarely occurs in women. Fortunately most cases of rosacea remain relatively mild and present only as an erythema with an occasional papulopustular component. At times a blepharitis and conjunctivitis may be present with rosacea, and less commonly there may be a keratitis, iritis, and episcleritis. In the cornea a pannus composed of fine vessels may be found along with infiltrations. With these changes ulcerations and scarring can occur.

Diagnosis

Differential diagnosis includes acne vulgaris, lupus* erythematosis and photoallergic reactions. Acne vulgaris occurs in a younger age group, usually is not limited to the flush areas and lacks the underlying erythema and telangiectasia. Lupus erythematosus lacks the papulopustular component and frequently shows some degree of atrophy. Photoallergic reactions are revealed by a history of onset and exacerbation following sunlight exposure. Such reactions are not limited to the face but may involve ears, neck, arms or any exposed area. As a rule this eruption lacks the pustular component of rosacea. At times, rosacea may be made worse by exposure to sunlight, a situation which can create confusion with both photoallergies and lupus erythematosus.

Etiology

The cause of rosacea is undetermined. Certain factors are known to aggravate rosacea, such as nervous tension, hot or spicy foods, coffee, alcohol and exposure to extremes of temperature. In addition, gastric or hepatic disease, focal infection, and menstrual irregularities have been implicated. However, in many cases none of these factors is demonstrable.

Treatment

Treatment of rosacea is essentially a management problem, for eradication of this condition cannot as yet be achieved. First, adequate cleansing with soap and water and the use of various drying preparations are helpful. The patient should be instructed to follow a bland diet with avoidance of foods already mentioned. In the pustular forms small dosages of systemic antibiotics such as tetracycline are often beneficial. Plastic surgery may be indicated in rhinophyma to reduce the deformity. The patient should be informed that the disease tends towards chronicity and that control of the clinical manifestations is often all that can be achieved, although especially in women there may be gradual spontaneous improvement.

Willard C. Peterson, Jr., M.D.
Minneapolis, Minnesota

*See Test Your Word Score Page 1757.

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Brief Summary

INDICATIONS: Include staphylococci, streptococci, pneumococci and gonococci. Recommended for acute, severe infections where adequate sensitivity testing has demonstrated susceptibility to this antibiotic and resistance to less toxic agents.

CONTRAINDICATIONS: Contraindicated in pre-existing liver disease or dysfunction, and in individuals hypersensitive to the drug.

PRECAUTIONS: CAUTION: USE OF THIS DRUG MAY PRODUCE ALTERATIONS IN LIVER FUNCTION TESTS AND JAUNDICE. CLINICAL EXPERIENCE AVAILABLE THUS FAR INDICATES THAT THESE LIVER CHANGES WERE REVERSIBLE FOLLOWING DISCONTINUATION OF THE DRUG.

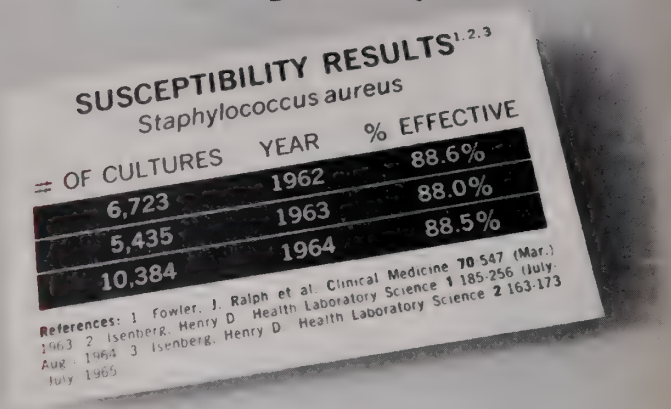
Not recommended for prophylaxis or in the treatment of infectious processes, which may require more than ten days continuous therapy. In view of the possible hepatotoxicity of this drug when therapy beyond ten days proves necessary, other less toxic agents should be used. If clinical judgment dictates continuation of therapy for longer periods, serial monitoring of liver profile is recommended, and the drug should be discontinued at the first evidence of any form of liver abnormality. When treating gonorrhea in which lesions of primary or secondary syphilis are suspected, proper diagnostic procedures, including dark-field examinations, should be followed. In other cases in which concomitant syphilis is suspected, monthly serological tests should be made for at least four months. When used in streptococcal infections, therapy should be continued for ten days to prevent the development of rheumatic fever or glomerulonephritis. The use of antibiotics may occasionally permit overgrowth of nonsusceptible organisms. A resistant infection or superinfection requires re-evaluation of the patient's therapy. In the event such occurs with this drug the medication should be discontinued, and specific antibacterial and supportive therapy instituted.

ADVERSE REACTIONS: Although reactions of an allergic nature are infrequent and seldom severe, those of the anaphylactoid type have occurred on rare occasions.

Roerig

J.B. ROERIG DIVISION
CHAS. PFIZER & CO., INC.
235 EAST 42nd STREET
NEW YORK, N.Y. 10017

In vitro
susceptibility results
with TAO® (triacetyl-
oleandomycin)
in *Staphylococcus aureus* cultures,
as shown in
studies of
antibiotics.



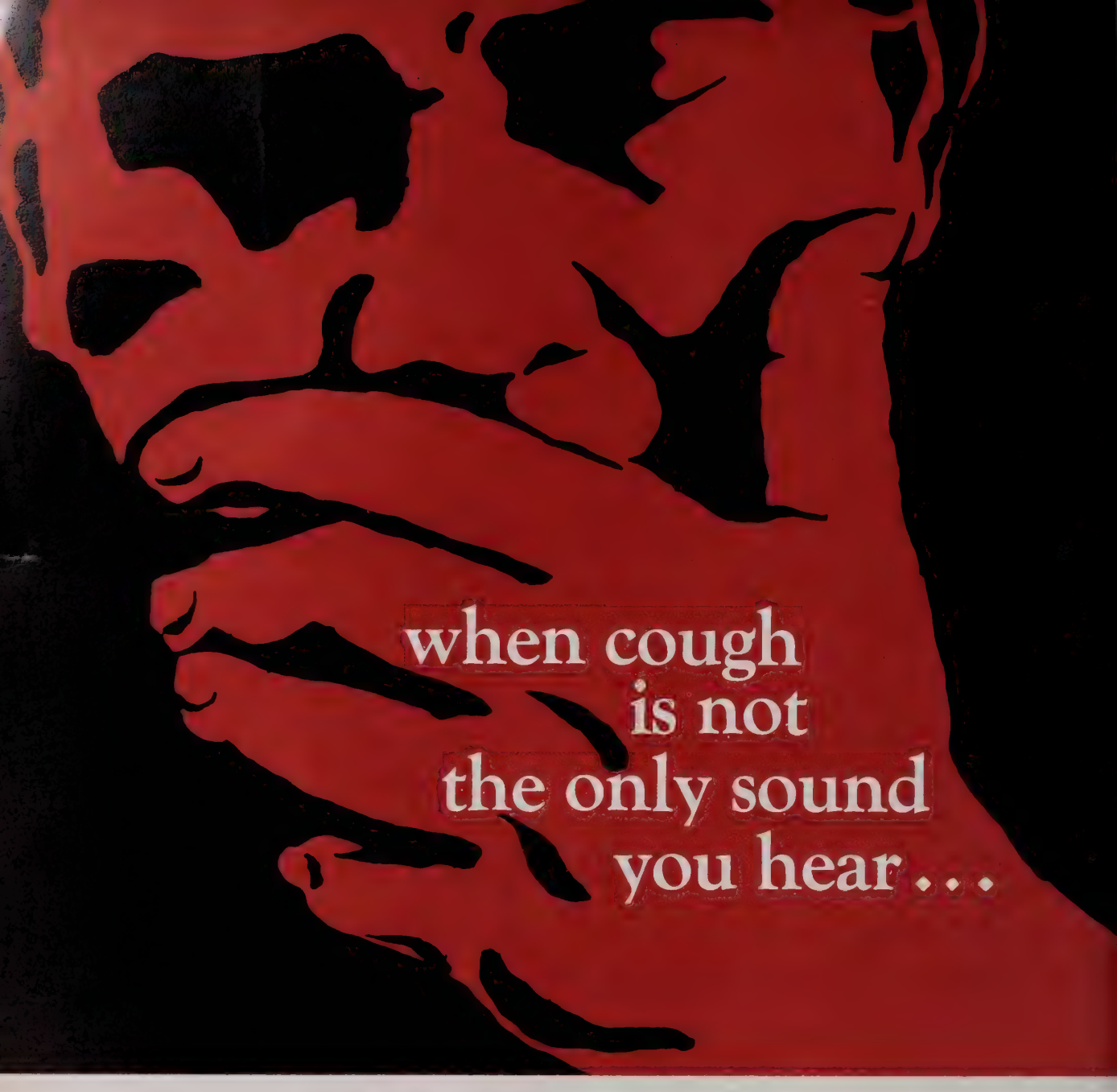
SUSCEPTIBILITY RESULTS[1,2,3]
Staphylococcus aureus

# OF CULTURES	YEAR	% EFFECTIVE
6,723	1962	88.6%
5,435	1963	88.0%
10,384	1964	88.5%

References: 1 Fowler, J. Ralph et al. Clinical Medicine 70 547 (Mar.) 1963 2 Isenberg, Henry D Health Laboratory Science 1 185-256 (July-Aug.) 1964 3 Isenberg, Henry D Health Laboratory Science 2 163-173 July 1965

TAO® (triacetyl-
oleandomycin)
is a macrolide antibiotic, for use only in
the treatment of acute severe
infections where adequate
sensitivity testing has
demonstrated susceptibility
to this antibiotic and resistance
to other less toxic agents.





OMNI-TUSS® b.i.d.

. . . **because** OMNI-TUSS is indicated for cough associated with upper respiratory tract infections, bronchitis, bronchiectasis, bronchial asthma, emphysema, sinusitis and rhinitis, hay fever, or other allergic conditions. Any of these conditions may exhibit the general symptom syndrome—coughing, wheezing, bronchospasm, and tenacious mucus—which may benefit from the antitussive, bronchodilative, antihistaminic, and expectorant action of Omni-Tuss.

The therapeutic usefulness of Omni-Tuss is enhanced by a unique resin complex formulation providing the clinically desirable advantages of: (1) uniform drug availability throughout an extended period, (2) 8 to 12 hours of symptomatic control, (3) minimal dosage requirement, (4) minimal side effects.

Economical, efficient **b.i.d.** dosage—extremely well-tolerated by children, 6-12, and adults.

'Omni Tuss' Suspension: Each teaspoonful (5 cc.) contains 10 mg. codeine (Warning: May be habit-forming), 5 mg. phenyltoloxamine, 3 mg. chlorpheniramine, 25 mg. ephedrine, all as cation exchange resin complexes of sulfonated polystyrene, and 20 mg. guaiacol carbonate.

Available on prescription only. Class X exempt narcotic. Permissible on oral prescription.

Dosage: *Adults:* 1 teaspoonful (5 cc.) q12h.
Children (6-12 *years*): ½ teaspoonful q12h.

Side Effects: Minimal, but when encountered may include jitteriness, nausea, drying of mouth, insomnia, constipation, which disappear upon adjustment of the dose or discontinuance of treatment.

Precautions and Contraindications: For complete detailed information, refer to package insert or official brochure.

Strasenburgh

Strasenburgh Laboratories Division
Wallace & Tiernan Inc., Rochester, N.Y.

Advances

The Choice of Antibiotics in Management of Bacteremia and Shock*

ALTHOUGH ALMOST any bacterial species can produce bacteremia under certain circumstances, some species are more frequently responsible.[1,2] It is the antibacterial drugs employable against these more frequently responsible bacterial species that are considered here.

Bacteremic shock refers to peripheral vascular collapse complicating bacterial invasion of the bloodstream. Although this type of shock is often emphasized as complicating bacteremia due to gram-negative bacilli,[1,3-13] it may also complicate other bacteremias, such as staphylococcemia and meningococcemia.

Some Principles of Management

Results of blood cultures and in-vitro† bacterial inhibition tests are mainly of retrospective value in the management of bacteremia, because antibacterial therapy often is begun empirically before such data are available. To postpone therapy until the results of such tests are reported would mean a delay of 24 to 48 hours and an increased chance of mortality.

The principles of antibacterial management of patients having bacteremia can be summarized as follows: (1) When cultures of blood are reported to grow bacteria, or when samples of blood for microbiologic study have been obtained from a patient suspected clinically of having bacteremia, antibacterial treatment is initiated empirically. (2) Reevaluation is made if in-vitro bacterial inhibition tests later indicate less than optimal choice of an antibacterial regimen, but the use of the regimen is continued unaltered if the patient is doing well. (3) The regimen is administered in adequate dosage for a sufficient time.

*Read at the meeting of the Minnesota State Medical Association, Rochester, Minnesota, May 12 to 15, 1968.

†See Test Your Word Score Page 1757.

Pathogens and Regimens

A general summary of pathogens and regimens is shown in Table 1 and the dosage of the applicable drugs is given in Table 2. The drugs are listed in order of choice to parallel the severity of the infection, and, generally, those in decreasing order are somewhat less effective or are more likely to be toxic. Of course, in some cases, several agents are recognized as being effective. In certain instances, a drug is preferred because the physician himself has had greater experience with it. Other drugs not listed may show some activity against a given bacterial species. Also, the antibacterial regimen selected for use in a given instance may reflect such factors as the patient's general condition and resistance, his allergic diathesis, and his ability to accept the regimen by the route designated.

In general, combinations of drugs should be reserved for situations that demand treatment while microbiologic data are awaited, for polymicrobic infections, and for instances of bacteremia wherein there are indications that an enhanced effect is possible.

Staphylococcal Bacteremia

In patients having staphylococcal bacteremia, certain antistaphylococcal drugs that have been effective in the past are infrequently employed at present, largely because the unavailability of microbiologic data—especially the results of in-vitro bacterial inhibition tests—often results in the use of a given drug and its continued use thereafter when the patient responds well. If such data were more speedily reportable, perhaps one of these alternative drugs could be employed in a given situation and there would be less concern about emergence of bacterial strains resistant to the drugs more commonly used at present.

The best treatment of staphylococcal bacteremia remains pencillin G therapy, provided the organisms are susceptible to it. However, as is well known, the number of staphylococci resisting the action of penicillin G makes it imperative to use other drugs in the empiric management of serious staphylococcal infections. Consequently, in cases wherein the patient is not allergic to the penicillins and in whom there are clinical or cultural indications that a staphylococcus is the cause of bacteremia, the physician commonly administers a penicillinase-resistant penicillin, such as methicillin, oxacillin, or nafcillin, at least until adequate microbiologic data become available. When these drugs are not applicable, as in patients who have a known allergy to the penicillins, cephalothin may be tried. How-

TABLE I
ANTIBIOTICS OF CHOICE IN BACTEREMIA DUE TO INDICATED ORGANISMS

Organism	Antimicrobial agents		
	First choice	Second choice	Third choice
Staphylococcus aureus and staphylococcus coagulase-negative	Bactericidal effect: pencillin G or a penicillinase-resistant pencillin	Vancomycin or cephalothin	Kanamycin, ristocetin, bacitracin, or neomycin
	Bacteriostatic effect: erythromycin or lincomycin	Novobiocin	Chloramphenicol
Streptococcus pyogenes	Penicillin G	Erythromycin	Cephalothin or lincomycin
Streptococcus viridans (examples, *S. mitis, S salivarius*)	Penicillin G, alone or with streptomycin	Erythromycin	Cephalothin, lincomycin, novobiocin, or vancomycin
Enterococcus (example, *S. faecalis*); anaerobic streptococci; microaerophilic streptococci	Penicillin G or ampicillin with streptomycin or kanamycin	Vancomycin	Ristocetin or erythromycin-streptomycin
Diplococcus pneumoniae	Penicillin G	Erythromycin	Cephalothin or lincomycin
Neisseria meningitidis (intracellularis)	Penicillin G	Erythromycin	A tetracycline or chloramphenicol
Neisseria gonorrhoeae	Penicillin G	Erythromycin	A tetracycline
Shigella	Ampicillin	A polymyxin	Kanamycin or chloramphenicol
Escherichia	Ampicillin or cephalothin	A polymyxin	Kanamycin or chloramphenicol
Salmonella typhi	Chloramphenicol	Ampicillin	
Other *Salmonella* and *Arizona*	Ampicillin	Kanamycin	A polymyxin, a tetracycline, or chloramphenicol
Citrobacter	A polymyxin	Kanamycin	A tetracycline or chloramphenicol
Klebsiella	Cephalothin	A polymyxin	Kanamycin or chloramphenicol
Enterobacter	A polymyxin	Kanamycin	
Serratia	Kanamycin		
Proteus mirabilis	Penicillin G	Ampicillin	Cephalothin, novobiocin, kanamycin, or chloramphenicol
Proteus vulgaris, P. morganii, and *P. rettgeri;* and *Providence*	Kanamycin	Chloramphenicol	Cephalothin
Pseudomonas	A polymyxin		
Mimeae (Mima polymorpha and *Herellea vaginocola)*	A tetracycline and either kanamycin or a polymyxin		
Bacteroides	A tetracycline	Chloramphenicol	Penicillin G or cephalothin
Data Insufficient to Generalize Regarding Management of Certain Pathogens (Alcaligenes, Flavobacterium, Moraxella, and so forth)			
Clostridia	Penicillin G	Erythromycin	A tetracycline
Listeria monocytogenes	Penicillin G	A tetracycline	Erythromycin

ever, some workers would point out that vancomycin is an effective antistaphylococcal drug, and would choose it over cephalothin. Cephaloridine is not considered under these circumstances, because it is not recommended for use unless in-vitro bacterial inhibition tests indicate its applicability; also, dichotomies between in-vitro testing and in-vivo achievability may make cephaloridine a somewhat hazardous antistaphylococcal drug. Under present circumstances, erythromycin, lincomycin, and novobiocin have infrequent use but might have increased use if their in-vitro applicability were known earlier in the course of the infection. Kanamycin, ristocetin, and chloramphenicol also have infrequent use as anti-

TABLE 2
DOSAGE OF ANTIBIOTICS IN BACTEREMIA

Agent	Route of administration		
	Oral	Intramuscular	Intravenous
Penicillin G (benzyl penicillin), and penicillin V or phenethicillin	Penicillin V or phenethicillin, 200,000 units (125 mg)-800,000 units 4-6 times daily*	Aqueous crystalline penicillin G, 4,000,000-12,000,000 units daily	Penicillin G, 6,000,000 units or more
Methicillin		4-6 gm/day in 4-6 divided doses	4-24 gm/day in 4-12 divided doses
Oxacillin	2-6 gm/day in 4-6 divided doses*	4-6 gm/day in 4-6 divided doses	4-24 gm/day in 4-12 divided doses
Cloxacillin	1-6 gm/day in 4-6 divided doses*	Commercially unavailable in USA	Commercially unavailable in USA
Dicloxacillin	1-3 gm/day in 4-6 divided doses*	Commercially unavailable in USA	Commercially unavailable in USA
Nafcillin	2-6 gm/day in 4-6 divided doses*	4-6 gm/day in 4-6 divided doses	4-24 gm/day in 4-12 divided doses
Ampicillin	2-6 gm/day in 4-6 divided doses*†	4-6 gm/day in 4-6 divided doses	4-12 gm/day in 4-12 divided doses
Streptomycin	Poorly absorbed	2 gm/day in 2 divided doses not to exceed 2 wk or 1 gm daily in 2 doses not to exceed 4 wk	
Kanamycin	Poorly absorbed	1-1.5 gm/day in 2-3 divided doses	1 gm/day in 2 divided doses
Tetracyclines	2 gm/day in 4 divided doses*†	Not recommended	1-2 gm/day in 2-4 divided doses
Chloramphenicol	3 gm/day in 6 divided doses*	3-4 gm/day in 3-4 divided doses	2-4 gm/day in 2-4 divided doses
Erythromycin	2 gm/day in 4 divided doses*	Not recommended	2-4 gm/day in 2-4 divided doses
Novobiocin	2 gm/day in 4 divided doses*	2 gm/day in 2 divided doses	2 gm/day in 2-4 divided doses
Lincomycin	2 gm/day in 4 divided doses*	1,200-1,800 mg/day in 2 or 3 divided doses	1,200-1,800 mg/day in 2 or 3 divided doses
Polymyxin B	Poorly absorbed	150-200 mg/day in 3 or 4 divided doses	150-200 mg/day in 1 or 2 divided doses
Colistin	Poorly absorbed	100-300 mg/day in 2 or 3 divided doses	100-300 mg/day in 1 or 2 divided doses
Vancomycin	Poorly absorbed		2 gm/day in 2-4 divided doses
Ristocetin	Poorly absorbed		2-4 gm/day in 2 divided doses
Cephalothin	Poorly absorbed	4-6 gm/day in 4-6 divided doses	2-6 gm/day in 4-6 divided doses

*Oral route not recommended in initial therapy.
†Dosage applicable to chlortetracycline, oxytetracycline, and tetracycline.

staphylococcal drugs, and their potential ability to cause toxic effects will probably continue to militate against their more widespread use.

As a generalization, antibacterial therapy of bacteremia due to staphylococci, like that due to most other bacterial strains, should be continued until the patient has been afebrile for at least 72 hours and three successive blood cultures have been negative.

Streptococcal Bacteremia

This condition has been studied by members of our group,[1] and a group A beta-hemolytic streptococcus organism *(Streptococcus pyogenes)* was responsible in about 50% of cases. Group D streptococci or enterococci, such as *S. faecalis,* were causative in about 30% of cases, whereas alpha-hemolytic or viridans streptococci, such as *S. mitis* and *S. salivarius,* were largely responsible in the remainder. Bacteremia due to anaerobic and microaerophilic strains of streptococci is infrequent.

In the treatment of bacteremia due to *S. pyogenes,* some workers give one million units of benzyl penicillin intramuscularly or by intermittent intravenous injection every four to six hours; other workers give larger amounts of the drug by continuous intravenous administration. In bacteremia due to *S. mitis* and kindred organisms, my colleagues and I are currently investigating a regimen of 1 gm of streptomycin given intramuscularly, plus 20 million units of benzyl penicillin given intravenously, per day; but some workers believe that streptomycin is not required in these infections. Because most strains of enterococci and anaerobic and microaerophilic strains of streptococci are more resistant to penicillin G than are other streptococci, we usually institute the same regimen outlined for infection due to *S. mitis* and allied organisms and increase the amount of benzyl penicillin in increments of 10 million units until the serum bactericidal test reveals total killing in a dilution of one to four or greater. In enterococcal bacteremia, some workers prefer kanamycin to streptomycin. There are preliminary indications that ampicillin may be as effective as streptomycin-penicillin G as an anti-enterococcal regimen. An amount of 6 gm or more of ampicillin should be given daily by a parenteral route, preferably intravenously; streptomycin or kanamycin may further enhance the effect of ampicillin.

In patients allergic to the penicillins, such antibiotics as cephalothin, erythromycin, lincomycin, or a tetracycline may be applicable in cases of bacteremia due to *S. mitis* or kindred organisms. These drugs, excepting the tetracyclines, are also considered in bacteremia due to *S. pyogenes;* about 40% of strains of *S. pyogenes* resist the action of the tetracyclines. A considerable number of enterococci and anaerobic and microaerophilic strains of streptococci resist the action of the alternative drugs, and the physician may have to rely on such antibiotics as vancomycin or ristocetin.

Pneumococcal Bacteremia

In cases of pneumococcal bacteremia, penicillin G is the drug of choice; the route of administration and daily amount, which may be several million units, are dependent in part on the presence or absence of associated endo-

TABLE 3

Classification of the Family Enterobacteriaceae*
(Adapted From Edwards and Ewing)[14]

Tribe	Group
Escherichieae	*Shigella*
	Escherichia (*E. coli,* including *Alkalescens-Dispar*)
Salmonelleae	*Salmonella*
	Arizona
	Citrobacter (formerly *E. freundii* and including *Bethesda-Ballerup*)
Klebsielleae	*Klebsiella*
	Enterobacter (formerly *Aerobacter*)
	E. cloacae
	E. aerogenes
	E. liquifaciens
	E. hafniae (alvei)
	Serratia
Proteeae	*Proteus*
	P. mirabilis
	P. vulgaris
	P. morganii
	P. rettgeri
	Providence
	P. alcalifaciens
	P. stuartii
Edwardsielleae	*Edwardsiella*
	E. tarda

*The term "paracolon" or paracolobactrum is not found in this classification; organisms in this group are assigned positions among the Enterobacteriaceae as follows: *P. aerogenoides* as *Enterobacter hafniae; P. intermedium* as *Citrobacter* group; *P. arizoneae* as *Arizona* group; *P. coliforme* as *E. coli;* and Paracolon 29911 or *Proteus inconstans* as *Providence* group.

carditis or meningitis. In patients allergic to the penicillins, a drug such as cephalothin, erythromycin, or lincomycin may be given. Because some strains of pneumococci are resistant to the tetracyclines, use of these drugs in pneumococcal infections, without in-vitro susceptibility tests indicating their applicability, may be hazardous.

Neisserian Bacteremia

This type of bacteremia is most commonly due to *Neisseria meningitidis,* the management of which is virtually inseparable from that of meningococcal meningitis. Benzyl penicillin in amounts of one million units every two to four hours by intramuscular injection may be used, but even larger amounts have been given per day intravenously. Because a number of strains of meningococci are resistant to the sulfonamides, these drugs cannot be relied on for initial management. *N. gonorrhoeae* rarely succeeds in invading the bloodstream, but large doses of penicillin G are recommended if invasion does occur.

Bacteremia Due to Gram-Negative Bacilli

This condition is most frequently due to organisms belonging to the family Enterobacteriaceae. In Table 3 there is a classification of the Enterobacteriaceae, adapted from Edwards and Ewing.[14] If the biochemical methods advocated by Edwards and Ewing are employed for isolating, grouping, and, in many cases, identifying members of the Enterobacteriaceae, differences will be found in the incidences of individual pathogens on comparison with those found in older studies based on other classifications. However, these differences are minimal and should not result in significant problems. Douglas and coworkers[15] have contributed helpful data regarding the laboratory diagnosis of infection due to the Enterobacteriaceae.

The comparative incidence of bacteremia due to *Shigella* should remain unchanged, and *Escherichia* remains the most common causative organism in the family.

The incidence of bacteremia due to *Salmonella* and *Arizona* should not be significantly changed, whereas that due to *Citrobacter* probably will be in the neighborhood of 2 to 3%.

Bacteremia due to the Klebsiella-Enterobacter-Serratia group is second in incidence only to *Escherichia.* Of this group, *Klebsiella* causes about 80% of clinical infections, whereas *Enterobacter* is responsible for approximately 15%, with *Serratia* causing the remainder.

Bacteremia due to *Proteae* is third in incidence, and that due to the Proteus group is far more common than that due to the *Providence* group organisms. Of the *Proteus* group species, the indole-negative *P. mirabilis* causes 70 to 80% of clinical infections, while the indole-positive *P. vulgaris, P. morganii,* and *P. rettgeri* cause the remainder.

Bacteremia due to *Edwardsiella* is rare and probably accounts for less than 1% of cases due to the Enterobacteriaceae.

For convenience, in addition to the Enterobacteriaceae, certain other gram-negative bacilli will be considered at this time (Table 4). These gram-negative bacilli, which are not members of the Enterobacteriaceae, are being considered concurrently, because antibacterial therapy when given empirically must be designed with these additional bacilli in mind. Bacteremia due to *Pseudomonas,* in recent years, has gradually attained an over-all incidence higher than that due to *Proteus* in some institutions. The other pathogens listed in Table 4 are not common causes of bacteremia, but a special word appears in order regarding bacteremia due to *Bacteroides.* Failure to obtain anaerobic cultures of the blood may conceal the fact that bacteremia due to *Bacteroides* may be present. In two thirds of our patients with such bacteremia, incubation times ranged from five to 20 days.

Before consideration is given to possible antibacterial regimens that may have empiric

TABLE 4
Some Gram-Negative Bacilli Other Than the Enterobacteriaceae

Pseudomonas
Mimeae
Herellea vaginocola (*B. anitratum*)
Mima polymorpha
Alcaligenes
Flavobacterium
Moraxella
Bacteroides

use in patients about whom knowledge of in-vitro inhibition tests is lacking, it may be well to discuss those drugs to which gram-negative bacilli are most likely to be susceptible on the basis of current data. As aforementioned, cephaloridine is not recommended for use unless in-vitro inhibition tests indicate its applicability; consequently, it will not be considered herein as a potential empiric regimen.

Shigellosis, unlike salmonellosis, almost always is a solely intraluminal enteric infection; however, about 50 cases of *Shigella* bacteremia have been documented to date. Because of increasing drug resistance of *Shigella,* ampicillin, a polymyxin (polymyxin B, colistin), kanamycin, or chloramphenicol may be applicable.

As a generalization, *Escherichia* organisms are susceptible to streptomycin and to the tetracyclines in about 50% of cases. Cephalothin inhibits about 70% of *Escherichia* organisms. These bacilli are susceptible to ampicillin, a polymyxin, kanamycin, or chloramphenicol in 80% or more of cases.

In regard to bacteremia due to *Salmonella typhi:* whereas chloramphenicol continues to be favored over ampicillin by some workers because of the more rapid control of fever and early symptoms, there are some data indicating that the use of ampicillin may result in fewer relapses. In bacteremia due to other *Salmonella* or *Arizona,* ampicillin, kanamycin, a polymyxin, or a tetracycline may be preferable. In *Citrobacter* bacteremia, a polymyxin, kanamycin, tetracycline, or chloramphenicol usually is indicated on in-vitro studies.

Of the Klebsiella - Enterobacter - Serratia group, *Klebsiella* organisms are most likely to be susceptible to the available antibiotics. Since *Klebsiella* organisms cause about 80% of clinical infections due to this group, this is a fortunate occurrence. As a generalization, strains of *Klebsiella* are susceptible to streptomycin, the tetracyclines, and ampicillin in 20 to 30% of cases; these bacilli are susceptible to chloramphenicol, kanamycin, the polymyxins, and cephalothin in approximately 80% of cases. Whereas a few exceptions occur, Enterobacter organisms are susceptible only to the polymyxins and kanamycin, and the susceptibility of *Serratia* bacilli is virtually restricted to kanamycin.

Among other drugs, penicillin G, ampicillin, cephalothin, novobiocin, kanamycin, and chloramphenicol are effective against *P. mirabilis.* Whereas cephalothin and chloramphenicol may prove active against certain indole-positive *Proteus* organisms and *Providence* bacilli, as a generalization, kanamycin is the drug of choice against these pathogens.

Edwardsiella organisms may be sensitive to several antibiotics, including the tetracyclines, chloramphenicol, kanamycin, and ampicillin.

In *Pseudomonas* bacteremia, a polymyxin is the preferred drug. In *Mimeae* bacteremia, a tetracycline combined with either kanamycin or a polymyxin is the regimen of choice. Despite the availability of newer drugs, a tetracycline generally is preferred in bacteremia due to *Bacteroides* organisms; chloramphenicol is also effective against these organisms; penicillin G and cephalothin may be active against certain strains of *Bacteroides.*

With these data in mind, the application of empiric antibacterial regimens in the management of bacteremia due to gram-negative bacilli can be considered.

Empiric antibiotic therapy is initiated on receipt of reports of blood cultures positive for gram-negative bacilli, or when bacteremia is likely after blood has been drawn for culture. In the past, a tetracycline combined with streptomycin, or alternatively, chloramphenicol and kanamycin, has been the preferred regimen under these circumstances by members of our group. More recently we have been investigating the combined use of cephalothin and a polymyxin. Other possible empiric regimens that may warrant investigation are cephalothin plus kanamycin and ampicillin given with kanamycin or a polymyxin.

In cases of bacteremia likely due to gram-negative bacilli, empiric administration of these regimens is preferred, because definitive microbiologic data will not be available for one or more days, and the broader antibiotic coverage is desirable. There is no dispute regarding the generalization that best results are obtained when the infecting bacilli are susceptible on in-vitro tests to the antimicrobial drugs employed, but the difficulty lies in

the unavailability of such data when the clinical status of the patient makes initiation of therapy necessary.

Empiric use of combined antibiotic therapy is not without disadvantages. These include the dual depressive effect on the gram-negative elements of the flora, making superinfection more likely. However, periodic study of the sputum and stools during therapy may reveal any floral changes and impending clinical superinfection. Streptomycin, kanamycin, the polymyxins, and possibly cephalothin are potentially nephrotoxic; excepting cephalothin, these drugs may cause a curariform effect that is manifested by respiratory depression and cardiac arrest. Chloramphenicol is hematotoxic. Streptomycin and kanamycin are ototoxic, but the latter is more likely to cause deafness. The polymyxins may also cause cerebellar ataxia and other neurologic complications. Ampicillin can cause anaphylaxis and the other untoward reactions characteristic of the penicillins and induces superinfection in about 5% of patients. Like ampicillin, cephalothin may induce superinfection from *Pseudomonas, Enterobacter, Bacteroides,* and sometimes other organisms. It appears unwise to employ drugs in combination, which share a significant toxic effect, because such use may enhance the likelihood of occurrence of such toxicity. As an example of this, kanamycin combined with a polymyxin might enhance the likelihood of a curariform reaction or a nephrotoxic effect.

With the advent of newer drugs, my colleagues and I have reevaluated our policy of employing combined antibiotic therapy. A polymyxin is inadequate as a single agent because *Serratia, Proteus, Providence,* and *Bacteroides* organisms are usually resistant to these drugs. Kanamycin has the disadvantage that a number of *Pseudomonas* and most *Bacteroides* are insensitive to it. Ampicillin is inactive against most *Klebsiella-Enterobacteria-Serratia* organisms, most *Proteus* bacilli that are indole-positive, most *Providence* bacilli, and *Pseudomonas* organisms. Cephalothin is not active against *Enterobacter-Serratia* organisms, many *Bacteroides,* most indole-positive *Proteus* and *Providence* bacilli, and is usually inactive against *Pseudomonas.* To date there is no single drug available that assures complete "coverage" against gram-negative bacilli.

Except for *Pseudomonas* organisms, the chloramphenicol-kanamycin regimen gives excellent "coverage" against gram-negative bacilli, whereas cephalothin, when combined with a polymyxin that remedies this defect, gives less assurance that indole-positive *Proteus* organisms, *Providence* bacilli, and *Bacteroides* organisms are being effectively covered. Consequently, if there are special reasons to suspect that the pathogen is *Pseudomonas*—for example, in patients having underlying hematologic disease—a regimen containing a polymyxin is to be preferred. Also it is to be recalled that the chloramphenicol-kanamycin regimen is potentially more toxic than cephalothin combined with a polymyxin.

Clostridial Bacteremia

This may occur in patients with underlying hematologic disease and in those with neoplastic disease; but most such infections have been associated with postabortal or puerperal sepsis. Placing the patient in a hyperbaric chamber is essential. Penicillin G in massive doses is the antibacterial drug of choice, but some workers believe that a tetracycline also should be given. Surgical extirpation of a septic focus, blood transfusions, and polyvalent gas-gangrene antitoxin may also be considered.

Listeria Bacteremia

Although this type of bacteremia may complicate neoplastic disease and diabetes mellitus, it has a propensity to occur during pregnancy. Infection due to *Listeria monocytogenes* may cause bacteremia in the infant while the mother is asymptomatic or has had an influenza-like illness. Penicillin G, erythromycin, or a tetracycline is recommended.

Summary and Conclusions

Antibiotic therapy is begun empirically when report of blood cultures is received, or, in seriously ill patients, after blood is drawn for cultures. If the patient's condition and microbiologic data later indicate that such empiric therapy is unsatisfactory, it is modified accordingly. Use of specific antibiotics in the initial management of these patients is only theoretically possible because, practically, one

is often thwarted by lack of cultural proof of the pathogen and, almost always, of its in-vitro susceptibilities. However, these difficulties are not of such magnitude that the physician cannot devise adequate antibiotic therapy on an empiric basis. If such a regimen is not employed, or not employed early in the infection, the essential problem is not being attacked, and recovery is unlikely.

It should be emphasized that the physicians must guard against losing valuable therapeutic time while awaiting the results of laboratory procedures and belatedly diagnosing bacteremic shock when the patient has not responded to regimens more pertinent to noninfectious shock. If bacteremic shock is not diagnosed early and if adequate antibiotic therapy is not quickly initiated, no supportive treatment will have optimal effect.

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Heart Diagnosis in Ancient Egypt

When his Heart spreads out, behold the vessels of the Heart are with excrement.

When the Heart is sick, behold there is an Oppression of the Heart, or it is an Overflow of Blood which arises in the Heart. It falls down and approaches his diaphragm, while his Heart feels an aversion.

When his Heart is in its right place the Fat of the Heart is on the left side. It neither rises upwards nor falls downwards. It remains soundly in its place.

When his Heart trembles and there is much fat under his Left breast, behold it is his Heart which causes a little of the sinking because his disease is spreading.*

*Bryan, Cyril: The Papyrus Ebers, D. Appleton and Company, New York, 1931.

How Are You?

Don't tell your friends about your indigestion:
"How are you!" is a greeting, not a question.
—Arthur Guiterman

Pediatrics

The Battered Child Syndrome

Part 1—Medical Aspects

PREVENTION AND reporting of "battered" children are obviously important, but recognition of such cases by the physician remains an important first step in the institution of appropriate action. Our purpose is to aid the physician in the recognition of children who have been traumatized or neglected and who fall within the scope of the "Battered Child" laws. The cases presented here describe a spectrum of physical abuse from over-zealous spanking to infanticide, that have come to the attention of the authors since 1963, when the Minnesota "Battered Child" law was passed.

Table 1 presents a summary of eighteen cases. The patients in all but two cases were under age three. The assailant was presumed to be the parent in fourteen of eighteen of the cases. The clinical diagnoses ranged from "failure to thrive", rickets, multiple ecchymoses, burns, lacerations, dehydration, vomiting, diarrhea, multiple fractures, subdural hematomata, blindness, deafness, and seizures. Three of the eighteen children died as a direct result of physical abuse; ten had a previous history of assumed beating or physical neglect.

Worthy of special note for the recognition of such cases is that in sixteen of the eighteen children the history initially obtained was incompatible with the physical findings; and despite the frequent intimation that the lesions were spontaneous, no new lesions occurred while any of the patients were in the hospital.

Discussion

Incidence

Because of lack of recognition and/or failure of reporting, the real incidence of the syndrome is unknown. Retrospectively, the American Humane Association says there are over 10,000 such cases per year. In a prospective study, Holter and Friedman,[1] on two separate surveys, found that 10% of all children seen in an emergency room for injuries during given periods of time were victims of physical abuse. In New York City, over a one-year period, 706 cases of the "battered child" syndrome were reported.[2] It seems fair to assume that the incidence is probably much higher than the figures usually given.

Characteristics of Maltreatment

In many of the cases of maltreatment certain characteristics are present (Table 2). Most important of these is evidence of trauma which is disproportionate to the history given. The child with burns (especially cigarette burns), dislocations, fractures (often multiple), of the long bones—particularly if the trauma is in different stages of healing—should alert the physician to the likelihood of abuse. Often in addition to the causes of the trauma being historically vague, there is a history of previous episodes similar to the one with which the physician is presented. Of importance is that no new lesions occur after removal of the patient from the home environment. The patient is usually less than three years old. Other findings often present are poor nutrition, poor skin hygiene, irritability, and repressed personality. In Holter and Friedman's series[1] ingestions were commonly associated with the maltreatment syndrome.

Varieties of Abuse

The varieties of abuse and neglect range from food deprivation or a severe spanking to homicide. Usually only one child in the

TABLE I

Age *Race/Sex* *Chief Complaint*	*Past History*	*Findings*	*Assailant and Result*
3* years Negro/ Male "He was beaten"	Negative	Ecchymoses on left forehead, eye, thigh	Stepfather Cleared
14 years Caucasian/ Female "I was beat up"	Negative	Ecchymoses on face, upper arm	Mother's boyfriend Cleared
1 year Indian/ Female "Fever and cough for five days"	Removed once before because of "neglect", one sibling beaten	Ecchymoses over nose, under each eye; pneumonia; failure to thrive; recent fracture right tibia; abnormal EEG	Mother Improved, became very outgoing
5 years Indian/ Female Abandoned	Past history of being burned by mother when drunk. ER visits for pneumonia sibling of 5 and 6.	Granulation tissue; infected lesions scalp, finger, feet, pneumonia	Mother Resolved
3 years Indian/ Female Abandoned	Multiple ER visits, one for coat hanger injury to eye, another for fall down stairs sibling of 4 and 6	Cigarette burns on thighs; infected skin lesions	Mother Resolved
1 year Indian/ Female Abandoned	Sibling of 4 and 5 with past history of anemia and growth retardation	Multiple excoriations: scars, ulcers, ecchymoses on shoulders; anemia	Mother Resolved
1½ years Caucasian/ Male "Burn"	Admitted one week before secondary to too severe a spanking. Mother said she "lost control."	20% second degree burns from being held under a faucet of hot running water	Mother Burns healed
5 months Caucasian/ Female "Fell from chair"	Fracture of femur at 2 months; apneic episode of 45 minutes; no M.D. seen	Pale; skull had widened sutures; positive right subdural tap; seizures; retinal hemorrhages and decreased weight	Mother and father Resolved
17 months Caucasian/ Female "Diarrhea and vomiting"	URI, diarrhea	Numerous bruises, soft tissue swelling forehead, scratches over left cheek; dehydrated; otitis	Unknown Resolved
8 months Caucasian/ Male "Not gaining weight"	One previous admission; pin in uretera	Rickets, hematomata left thigh, swelling both arms, swelling right side skull fracture, fracture right ulna, fracture left humerus, fracture right acromion	Both parents Gained weight, developed mentally, gained milestones, rachitic rosary and thickened wrists disappeared, fractures healed.

TABLE I (Continued)

Age *Race/Sex* *Chief Complaint*	*Past History*	*Findings*	*Assailant and Result*
1½* years Caucasian/ Male "He woke up bleeding"	Three previous hospitalizations; multiple fractures, bruises, subdural	Lacerated scalp linear, punctate wounds on both feet, ecchymoses on face	?Both parents —probably mother Lesions healed
6 months Caucasian/ Male "Fell out of crib"	Police called to home one week prior to admission because neighbors complained that mother was beating the child	Fractured skull, subdural ecchymoses of face, lacerated lip	Father Craniotomy, resolved
1 month Caucasian/ Female Seizures, cyanosis, vomiting	Other siblings battered	Positive subdural taps; irritable hydrocephalic	Unknown Shunt
2 months Caucasian/ Male "Vomiting and sleepy"	Negative, one other sibling removed secondary to beatings	Parietal eggshell skull fractures, subdurals, hydrocephalus, cortically blind and deaf	Mother Craniotomy, blind and deaf
2 years Caucasian/ Male "Fell down stairs"	Negative	Distended abdomen, paracentesis milky bile fluid	Father Surgery—infarcted liver from trauma
1¾ years Caucasian/ Female "Vomiting: not gaining weight"	Subdurals, assymetry of head, papilledema, eye ground hemorrhage; hydrocephalus; development retarded; x-rays showed no fractures, long bones; craniotomy evacuated, subdurals	Marasmic; hemorrhagic mouth, head and trunk; ecchymoses of leg; optic atrophy; blind; serum sodium 191 perustical elevation in right tibia, right humerus 3 weeks old; seizures	"Struck by sibling" Died in spite of treatment; at autopsy: skull fracture, hemorrhage, old subdural psoas abscess
4 months Mexican/ Female "Unconscious"	Negative	Skull fractures; subdurals	Unknown—Had been in three foster homes in one week. Died
16* months Negro/ Male "He fell out of his highchair"	NIL—Sibling brought in this year—battered	Opistotonic; dilated right fixed pupil; right anterior forehead covered with bruises; ecchymoses over posterior scalp, right upper quadrant of abdomen; abrasions nose and neck; linear ecchymoses right arm; bruises from scapulae to popliteal spaces; papilledema and hemorrhages in eye	"Aunt" Craniotomy—died

*See Case Reports

family is the target; but by no means is this always the case. (Of interest here is that three cases (Table 1) were all from one family, yet a fourth sibling was completely spared.) Hairbrushes are a common instrument used to inflict physical abuse; but fists, straps, electric cords, TV aerials, ropes, rubber hoses, fan belts, sticks, bottles, broom handles, baseball bats, chair legs, paring knives, and screwdrivers are also employed. These children are also submitted to burns, strangling, suffocation, stabbing, biting, shooting and electric shock. They may be violently thrown, with arms and legs used as handles. Cases have been reported where pepper was stuffed in the pharynx, suffocating the victim.[3] One child was reported to have been buried alive.[3] Attempts have even been made to burn the corpses of the battered children.

In a series of autopsies,[5] the causes of death listed included starvation, burning, gunshot wounds, asphyxia secondary to ligature, drowning, smothering, and carbon-monoxide poisoning. Also listed were stabbing, chopping with an ax, pounding with a hammer, and "squeezing to death." Almost all deaths have occurred in the home.

The "battered child" syndrome should be considered in all cases of childhood death where there is inadequate explanation for the extent of injury, or where the clinical picture is bizarre. Although the history most often obtained sounds outwardly reasonable, such as an accidental fall from a crib, table or sofa, accidental dropping during bathing, suffocation in the crib, and aspiration and assault by siblings, nevertheless the location, extent and type of injury incurred is unusual or improbable, considering the accident described. Also, a child is frequently brought to the physician with only a history of vomiting, fever or cough; lethargy or poor weight gain, with no explanation for obvious trauma.

TABLE 2

When to Consider a Diagnosis of Maltreatment

Subdurals
Bruises, cuts, abrasions disproportionate to the history
Burns—especially cigarette
Dislocations
Fractures, often multiple—especially of long bones
Above in *different stages of healing*
Causes of trauma in question
History of previous episodes
No new lesions during removal from home
Less than three years old
Failure to thrive
Poor skin hygiene
Irritability
Repressed personality
Ingestions

Differential Diagnosis

The major differential diagnoses in cases of multiple or recurrent fractures include osteogenesis imperfecta, hypophophasia, hyperuricemia with self-mutilation, scurvy, neonatal syphilis, infantile cortical hyperostoses, sensory deficit or indifference to pain. Other disease possibilities to be considered are rickets, celiac disease, osteomyelitis, bone tumors, blood dyscrasias, congenital coxa vera, meningitis, infectious diarrhea, tuberculosis, congenitally dislocated hip, and poliomyelitis.

Early recognition of the "battered child" and removal from the traumatic environment are of paramount importance for salvage of these patients, since the rule, rather than the exception, is that the patient will return, either further traumatized or dead. In one series, 10% returned dead. Other series report recurrent trauma in 30 to 50% of children.

Case Reports

Three cases are reported here to illustrate the range of injuries sustained by the "battered" children.

Case 1

A three-year-old negro male was admitted to Hennepin County General Hospital in February 1968 with a chief complaint by his mother that he "was beaten." His mother, a University of Minnesota student, was away from home at the time, leaving him in the care of his Caucasian stepfather. In response to being told to go to bed the patient defecated in his clothes and was then allegedly beaten by his stepfather. Physical examination revealed ecchymoses over the anterior forehead, the left eyelid, and both anterior thighs. X-rays of the skull and long bones were negative. There was no past history of beating.

Case 2

An eighteen-month-old Caucasian male was admitted to the University of Minnesota Hospitals in September 1967. Significant past history revealed that at 2½ months of age he had been admitted to a hos-

pital in Minneapolis with a seizure disorder. A diagnosis of bilateral subdural hematoma had been made and a craniotomy performed. Long-bone x-rays at that time had revealed periosteal new bone formations of both the left and right femurs and tibias, which were interpreted as evidence of healing fractures. The child's landlady had appeared and informed the attending physician that she and other neighbors had heard beatings going on through the walls.

The child had previously been admitted to the University of Minnesota Hospitals at the age of six months with the chief complaint of dehydration. Also stated in the history was that he had not been eating for three days and had been batting his head on his crib. Physical examination revealed a dehydrated, apathetic, frightened child. Thirty bruises were counted on his head and anterior chest. Scratches were present on his nose and chin; there was blood on his palate and a soft tissue swelling over the mandible. He had poor head control and difficulty in swallowing. (See Figures 1 and 2.) During the interview, it had been noted that the mother had a very flat affect and seemed quite unconcerned, and that the father was quite hostile. (He had previously been jailed for beating the mother.) No new lesions developed during the hospitalization, and the child was released to the custody of the Welfare Department for three months.

He was admitted again in August 1967, at 16 months of age, with the history that "he fell out of his crib," and that three days later he "suddenly" developed a mid-frontal swelling. On physical examination, multiple abrasions, scars, scratches, and bruises about the eyes and on the face were noted. He also showed mental and motor retardation. (Subdural taps done obtained 5½ cc of pink fluid on the right.) Psychological testing revealed a 12-month-old aptitude at 16-month chronological age; an electroencephalogram showed an abnormal sleep pattern with an irregular left frontal focus. No new lesions developed during the hospitalization. He was discharged to the family, but assigned clinic appointments were not kept.

In September 1967, at 18 months of age, he was re-admitted for a lacerated scalp. The history was given that he had been found bleeding in his crib, but the parents "had no idea" as to how he had cut him-

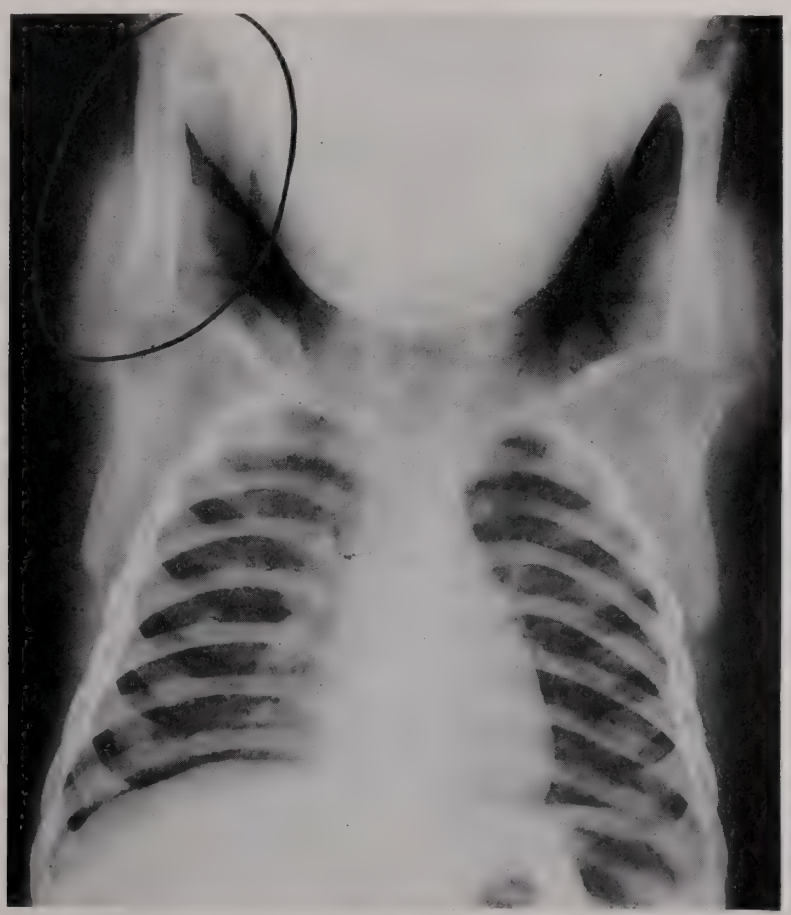


Fig. 1—Roentgenogram of Case 2, at age six months, revealing a healing fracture of the right humerus which is an older fracture than in Figure 2.

self. (They said he was a "head banger"; however, this habit had not been noted in the hospital.) During the interview the parents were very vague and inappropriate. They displayed a marked over-concern for a 2½ year old female sibling who, according to them, had "a high IQ," "never had a mark on her," and "had an emotional breakdown when he (her brother) came home." Physical examination at this time showed a scalp laceration, punctate linear scars on both feet, and a scar on the midback resembling a cigarette burn. Ecchymoses were present on the patient's face and arms.

Case 3

A sixteen-month-old negro male was brought into Hennepin County General Hospital in March 1968 by an "aunt" and a neighbor. The history was that he had fallen three days before and gotten a "bump on his head." He then allegedly resumed normal daily activity but the next day had acted "sleepy eyed." The morning before admission he was reported to have been "fine and ate a good breakfast." After the meal he had been placed on the floor and his aunt had left the room. When she returned, she noted that he was unconscious and unresponsive. The upstairs neighbor suggested that he must have climbed onto a chair and fallen onto his head, as the aforementioned swelling became larger. On further questioning, the aunt admitted that she had "spanked" him with a belt two days prior to admission and "may have hit his abdomen." It was later discovered that the "aunt" had given an alias, as had the neighbor. Both were prostitutes, as was the child's mother who was "looking for work in Indianapolis." Also, the "aunt" had been tried for shooting a boyfriend earlier in the year.

Physical examination showed an opistotonic male with dilated fixed right pupil and hemorrhages in both eye grounds. The left eye was deviated down and out. He responded only to deep pain and he was in extensor spasm. He had old bruises and abrasions over the right anterior forehead, ecchymoses over the posterior scalp, right eyelid and right upper quadrant of the abdomen, abrasions over the nose and scratches on the neck. There were linear ecchymoses over the left lower chest and left abdomen, parallel ecchymoses over the right upper arm, ecchymoses on the right lower arm, and continuous bruises from the posterior leg and popliteal area to the scapulae. Subdural taps could not be done as the sutures were closed; so he was taken to the operating room where trephinations were done bilaterally, with 75 cc of subdural clot being removed from the right. Marked cerebral edema was noted at surgery. He died the morning after admission.

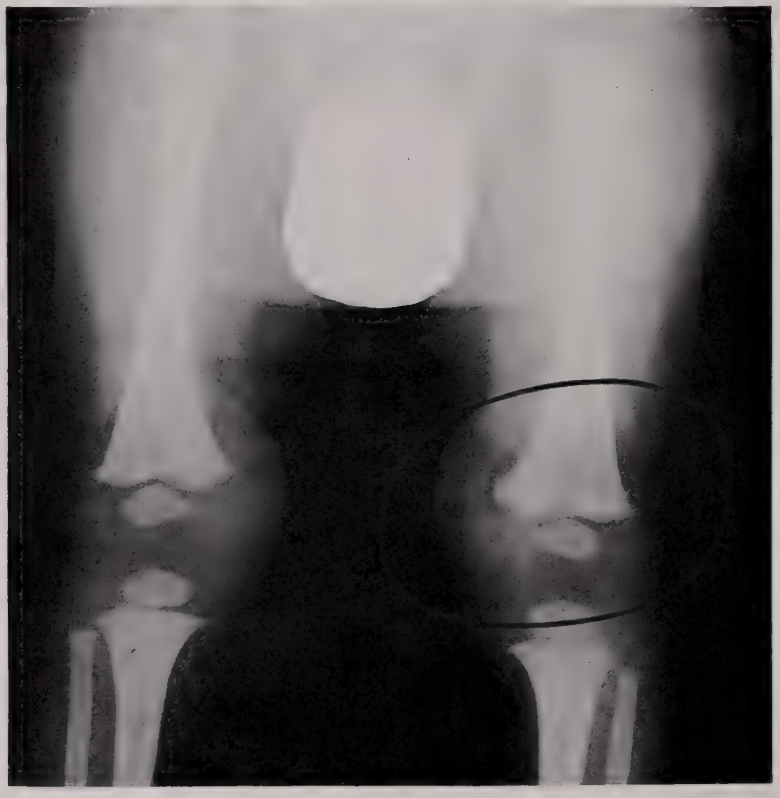


Fig. 2—Recent fracture of left femoral epiphyseal plate, taken at the same time as Figure 1.

Summary

The Battered Child syndrome occurs not infrequently and should be suspected when evidence of trauma is disproportionate to the clinical history. The varieties of abuse can be appalling.

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Battered Child Syndrome

A series of articles on the Battered Child Syndrome by Doctors Hugh D. Allen, Robert W. ten Bensel, and Richard B. Raile will be published in the following issues of MINNESOTA MEDICINE.

January—A discussion of the psychological and social aspects with consideration given to the parent, child, and health personnel.

February—Legal aspects will be discussed with emphasis on cases since the changing of the Minnesota State law in 1963. The physician's responsibility (moral and legal) and suggestions for development of a Battered Child law per se will be discussed.

March—A review of the syndrome and discussion of the future of children and the role of physicians.

School of Salerno

When to Bleed

The Heart and Liver, Spring @ Summers bleeding,
The Fall and Winter, hand and foot doth mend,
One veine cut in the hand, doth help exceeding
Unto the spleene, voyce, brest, and intrailes lend,
And swages griefs that in the heart are breeding.
—Regimen Sanitatis Salerni

Editor's note: The School advises that to benefit the heart and the liver, bleed the patient in the spring or summer; for the hands and feet, bleed in the fall or winter. Cutting one vein in the hand benefits the spleen, the voice, the breast, and the entrails; it even mitigates incipient grief.

It's the Law

Primer of Parliamentary Procedure*
The Tactics of Change

A *main motion* having been presented, seconded, and stated by the Chair, the assembly proceeds to act upon it. Discussion of the merit or lack of merit of the recommended action may now take place. Members may discuss and argue their various viewpoints before the society after individual recognition ("obtaining the floor") by the chair. Each member has the right to speak twice on the same question but may not make his second speech until all members who desire to speak for the first time have had opportunity to be heard.

During debate, changes in the *main motion* may be effected by certain *subsidiary motions.* The *main motion* may be altered in part or total by the motion *to amend,* and may take the form, "I move to amend the resolution by inserting the word *very* before the word *good.*" In other forms, the amender may move to "strike out" a certain word or words; to "strike out and insert;" to "substitute."

The motion to *amend* must be seconded and, after being stated in full to the assembly, it too becomes debatable. During discussion, the motion to *amend* may be amended, but only once, since amendments of the third order are cumbersome. After debate on the motion to *amend,* the chair puts the question (The motion to *amend*) and asks for the vote. If the vote is in the affirmative, the *amended* main motion becomes the question before the assembly. If a majority vote "No," the original main motion is again before the group.

A second tactic of change is the motion to *refer* or *commit* the main motion to a standing or special committee or individual. Like the motion to *amend,* the motion to *refer* requires a second, and when stated by the Chair, becomes debatable and amendable. If amended, the amendment is first voted upon, then the motion to *refer.*

At this point in our lesson a brief digression is in order so that we may introduce a discussion of the precedence or priority of motions. We have stated that only one *main motion* may be before the assembly at any time. Yet, in the above paragraphs, several motions have been considered in order. There is then a relationship between various motions providing a key to their individual entry into the parliamentary scheme. Thus, once a *main motion* is before the group, it may be *amended, referred, postponed, laid on the table,* etc. Basic to parliamentary procedure is this priority classification of secondary motions allowing the motion to *amend,* then the motion to *refer,* in that order, but not the reverse. Similarly the motion to *lay on the table* takes priority over to *amend* and to *refer,* and must be considered first by the Chair. Certain special motions such as *to adjourn* take precedence over all other motions and may even be in order when a vote has been ordered on the *main motion.* Time and space do not permit a full description of the priorities of various motions, but any manual of parliamentary procedure will readily produce this classification.

John Thomas, M.D.
Duluth, Minnesota

*See Minnesota Med 51:1508, 1968.

(To be continued next month)

It's going to be fun to watch and see how long the meek can keep the earth after they inherit it.—Frank Hubbard

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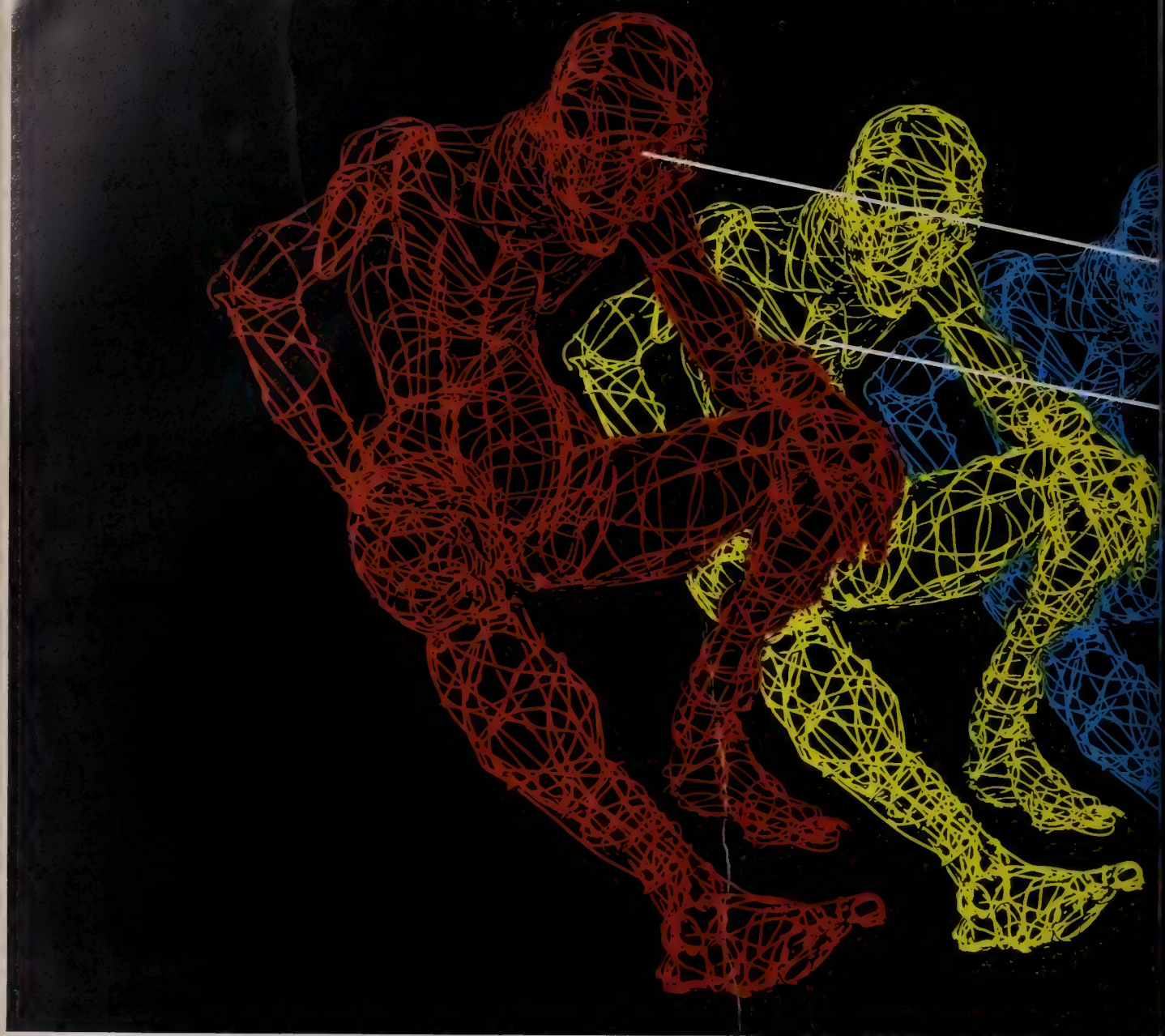
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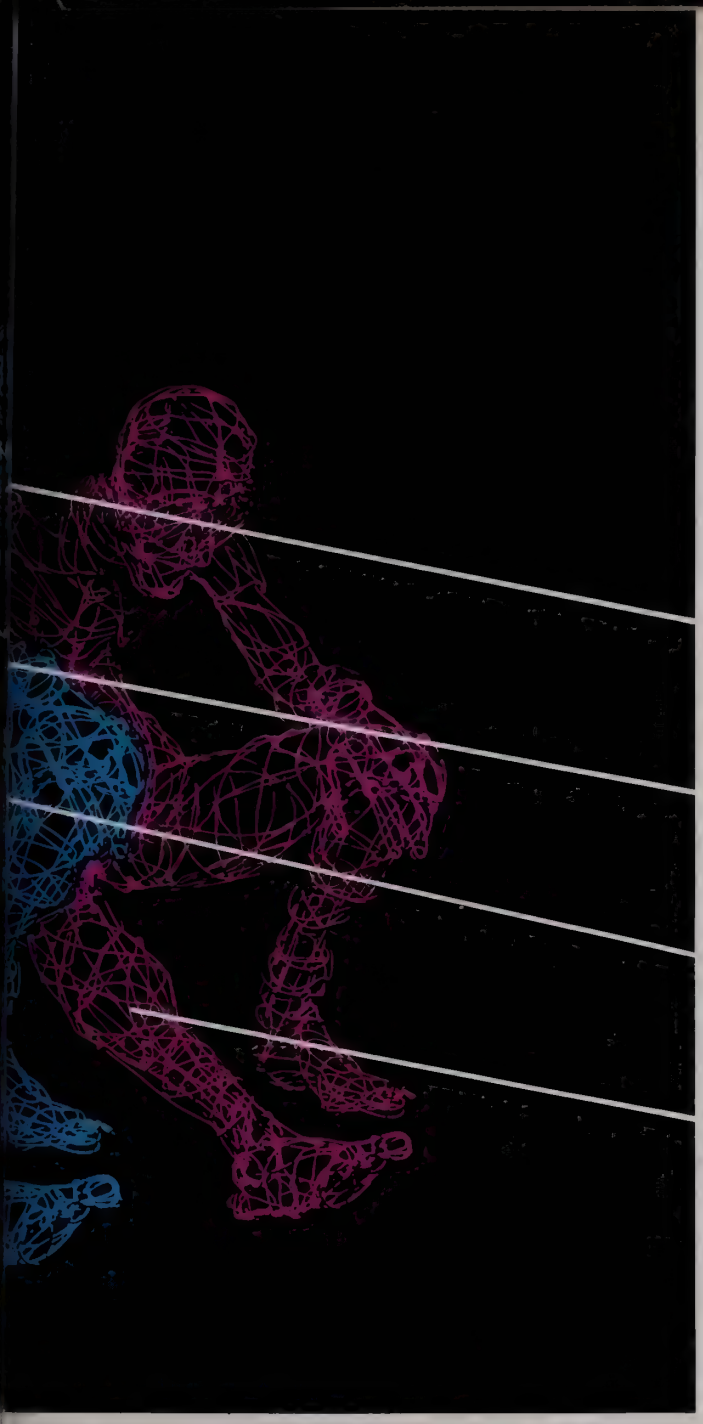
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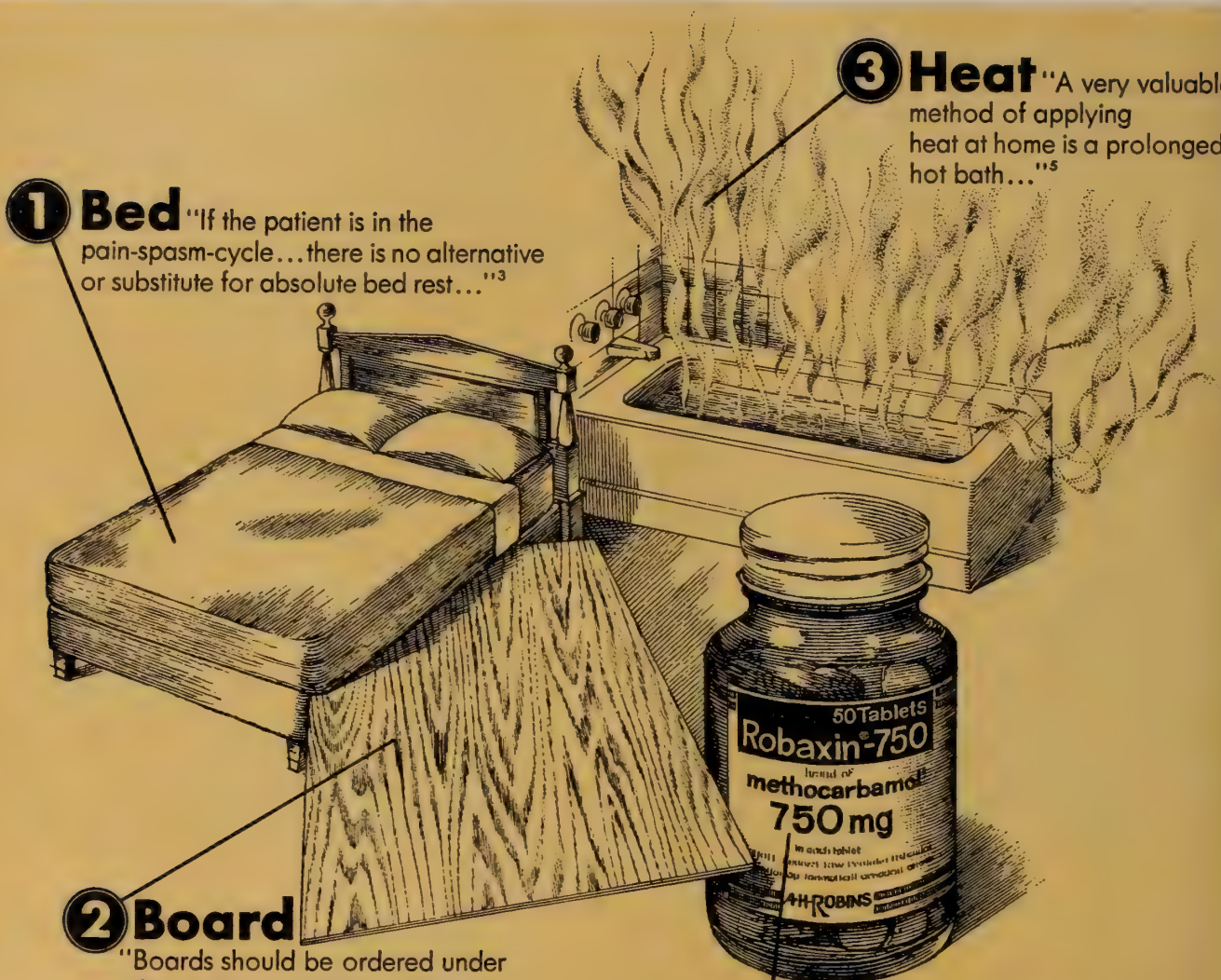
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References: (1). Godfrey, C.M.: Applied Therap. 8:950, 1966. (2). Gottschalk, L.A.: GP 33:91, 1966. (3). Rowe, M.L.: J. Occup. Med. 2:219, 1960. (4). Cozen, L.: South Dakota J. Med. 18:26, 1965. (5). Soto-Hall, R.: Med. Sc. 14:23, 1963. (6). Weiss, M. and Weiss, S.: J. Am. Osteopath. A. 62:142, 1962. (7). Feuer, S.G., *et al.*: New York J. Med. 62:1985, 1962.

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Grand Rounds

Pulmonary Arteriovenous Fistulae*

ROBERT N. NOTSKE, M.D.
Minneapolis, Minnesota

Historical

Pulmonary arteriovenous fistula is an abnormal communication between the pulmonary artery and the pulmonary vein, anywhere along the course of these structures from the main trunks to precapillary levels. Pulmonary telangiectasiae,† arteriovenous aneurysm, arteriovenous varix, cavernous hemangiomas, cirsoid aneurysms, pulsating angiomas are examples of the terms used to denote this abnormal vascular communication in the lesser circulation.

In the British Medical Journal of 1887 the following report appeared: "Doctor Churton showed the lungs from a boy 12 years of age in whom a loud roaring pulmonary systolic bruit and very highly accentuated second sound were present during life, with haemoptysis, epistaxis and dropsy. Four of the secondary branches in one lung, and three in the other, led to aneurysms as large as walnuts, filled with blood clot. . . ."[1] This is the first known description of a pulmonary arteriovenous fistula, but Churton did not appreciate the nature of the defect, calling it "multiple aneurysm of the pulmonary artery."

In 1917 Wilkens[2] gave a complete description of the clinical and autopsy findings in a sixteen-year-old girl with multiple pulmonary arteriovenous fistulas, but he also called it "a case of multiple pulmonary aneurysms." He described the epistaxis, cyanosis, dyspnea, clubbing of the fingers and toes, and telangiectasiae of the lips and tongue. There were murmurs in both axillae, and the chest x-ray showed densities in both lung fields. Wilkens demonstrated by dissection and injection multiple pulmonary arteriovenous fistulae of both lungs, one of which had ruptured into the pleural cavity. It

*Presented as a Medical Grand Rounds at Hennepin County General Hospital, January 16, 1968.
†See Test Your Word Score Page 1757.

should also be noted that this patient had hereditary hemorrhagic telangiectasiae.

Hemorrhagic telangiectasiae had been described in 1886 by Legg, and in 1887 by Chiari. It was Rendu in 1896 who first associated the tendency toward epistaxis with telangiectasiae occurring in families as a clinical entity.[3] In 1901 Osler[4] presented three cases of recurring epistaxis associated with multiple telangiectases of the skin and mucous membrane, and stated that Babbington and Rendu[3] had previously reported such cases. A few years later Weber[5] followed with further descriptions from his experience. This entity was thus termed "Osler-Weber-Rendu syndrome." Though the first cases of pulmonary arteriovenous fistula and many since were described as having telangiectasia of the mucous membranes and skin, they are not necessarily associated. The relationship between Osler-Weber-Rendu syndrome and pulmonary arteriovenous fistula is present in one third to one half of the cases described in the literature.[6]

The first case of arteriovenous fistula of the lung diagnosed clinically was reported in 1937 by Smith and Horton.[7] The patient was a forty-seven-year-old man who had complained of attacks of numbness, dizziness, convulsions and exertional dyspnea. He had been a "blue baby." Cyanosis and clubbing of the fingers and toes had been noted at twenty-three years of age while he was in the army, and again at forty years of age at the Mayo Clinic. He had been diagnosed as having polycythemia vera and treated with phenylhydrazine and by venesection without benefit. Chest x-ray revealed an abnormality in the base of the right lung, and a continuous murmur was heard over the lesion. Angiograms revealed that the density was vascular in nature.

The first patient with pulmonary arteriovenous fistula cured by operation was reported by Hepburn and Dauphine in 1942.[8] This twenty-three-year-old lady had been diagnosed as having a "leaky valve" in 1932, and in 1938 had been sent to a tuberculosis sanitarium for symptoms referable to the lung. She had also complained of dizziness, faintness, thick speech earlier in life. Chest x-ray disclosed a right lower lobe density. She also was noted to have clubbing, cyanosis, and polycythemia. Artificial pneumothorax was performed with no improvement. A right pneumonectomy was also performed, and the right lower lobe was found to contain a "cavernous angioma." A year later she was asymptomatic; the clubbing of the fingers and toes had receded; and she was pregnant and doing well.

Since that time many other cases have been reported and many successful resections recorded. In 1959 Bosher[9] reported 350 cases, 252 from the previous literature, with 98 new ones. In the interim the reports have dealt with more advanced techniques for diagnosis and more sophisticated techniques for resection.

The experience at Hennepin County General Hospital over the past ten years has resulted in two cases of pulmonary arteriovenous fistula. In the past five years there has been only one case. This patient was seen here this year.

Case Report

A 19-year-old Negro, separated, mother of four, was brought to the Emergency Ward because of the acute onset of a feeling that she was unable to move her legs. This lasted only a few minutes, and by the time she had arrived in the Emergency Ward she was totally asymptomatic. She had also noted a recent dry cough and easy fatigability. There had been no chills or fever. Her past hospitalizations had been for delivery of her children, and two months previously in a private hospital for "nerves." A chest x-ray disclosed a 4-cm. coin-

shaped lesion with a central clear area, located in the posterobasal segment of the left lower lobe. Physical examination was within normal limits.

Repeated sputum smears and cultures, skin tests, and chemical, hematological, and serological studies were within normal limits. Repeated chest films and planigrams showed no change in the lesion, which seemed to expand and contract with respiration. Three days after admission she noted another spell of not being able to move. A nurses' aide noted she had no obtainable pulse or blood pressure and that she appeared cyanotic. Within five minutes she had fully recovered. An electrocardiogram taken at this time disclosed depressed ST-T segments across the anterior precordium, and also in leads 2, 3, and aVF, with a depressed T in aVL. Ten days after admission her cardiogram disclosed non-specific ST-T changes in leads 2, 3, aVF, and now symmetric T wave inversion across the anterior precordium suggesting epicardial ischemia. These changes slowly reverted to normal over a six-week period. She had had similar, though less marked changes, one year previously just prior to her last delivery. A murmur could now be heard both in systole and diastole at the medial portion of the left base. Hgb. was 14 gm., with a normal white blood cell count and differential. Sedimentation rate ranged between 40 and 60 mm/hr. antistreptolysin titres, C-reactive proteins, lupus erythematosus clot tests, cold agglutinins, and viral studies, were within normal limits. Arterial oxygen tension ranged at rest between 50 and 60 mm. of Hg., and did not correct after breathing 100 per cent oxygen for fifteen minutes. After waiting for the electrocardiogram changes to return to a more normal pattern (eight weeks) a cardiac catheterization was performed. All pressure measurements were within normal limits. Angiocardiography disclosed a right-to-left shunt from the pulmonary artery to the pulmonary vein in the posterobasal segment of the left lower lobe. The coronary arteries appeared normal.

A thoracotomy was performed and revealed a large saccular, abnormal vascular communication. A segmental resection was performed. Postoperatively the patient developed a right-sided hemiplegia with aphasia. She has since recovered good motor function, but at this time is still aphasic.

Pathology

The wide variability of anatomic presentation of these pulmonary vascular abnormalities reveals that[9,10] on the one extreme, there may be multiple minute arteriovenous fistulae distributed through all lobes of both lungs, and on the other extreme, a single large saccular communication which often produces marked clinical manifestations. There may be a wide range of minute, small, or large fistulae, scattered or localized, in some instances producing little clinical difficulty, and in others marked symptoms. The configuration of the lesions varies considerably. The large size of the sac is often impressive, particularly when single, and the feeder vessels are usually limited to one or two large arteries.[9] "The channel is often sinuous and may be partly filled with clots. The arteries are usually thin-walled and dilated. The wall is often paper-thin, built up by hyalinized fibrous tissue, elastic fibers and remnants of smooth muscle cells. The intima may be unevenly thickened, partly covered by mural thrombi, and may show atheromatous lesions which are not uncommonly calcified."[10] In other instances, however, convoluted masses of dilated thin-walled vessels with multiple communications dominate the picture. In occasional instances an entire segment and even a lobe may be largely infiltrated and replaced by the pathologic process. "Cases have been described in which a varix of thin-walled vessels spreads out over the surface of the lung like a Medusa head."[9]

Pathogenesis

Pulmonary arteriovenous fistulae are frequently associated with other vascular anomalies. As previously mentioned, one third to one half of the cases in the literature have been associated with hereditary hemorrhagic telangiectasia. Some investigators still believe that the pure pulmonary form may represent a *forme fruste* of the systemic disease. "Pulmonary arteriovenous fistulae may be either acquired or congenital in origin, the latter being much more frequent than the former."[6] The occurrence of a congenital lesion may

be readily explained by the aberrant development of arteries and veins from a common capillary plexus. Although frequently not apparent at birth, these lesions tend gradually to increase in size as a result of inadequate vascular wall formation and constant exposure to direct pulmonary artery pressures. The origin of acquired fistulae, however, is much more complex.[6] Usually no known stimulus has been identified. A recent report described multiple pulmonary arteriovenous fistulae believed secondary to metastatic carcinoma of the thyroid.[11] Other reports have suggested acquired fistulae from pulmonary schistosomiasis[12] and long-standing hepatic cirrhosis.[13]

Distribution

Tables 1 through 4 summarize the anatomic distribution of pulmonary arteriovenous fistulae in 328 cases described by Bosher.[9] Sixty-four per cent were thought to have single lesions. The higher percentage of patients with single lesions reflects the detection of relatively asymptomatic and acyanotic patients through routine x-ray examination.

In Table 3 the cases are listed according to the number of lesions reported per case. Sixty-eight are categorized as "multiple" or "not specified" because of vague or indefinite description. The majority of this unspecified group, however, undoubtedly had more than three lesions. In 30 cases of the entire group of 117, no more than two lesions were found.

TABLE 1
Number of Cases*

Single arteriovenous fistula	212
Multiple arteriovenous fistulae	117
Total cases	328

*Modified from Bosher et al., Surg 45:91, 1959.

TABLE 2
Location of Single A-V Fistulae*

Left upper lobe	36
Left lower lobe	56
Right upper lobe	17
Right middle lobe	34
Right lower lobe	50
Not specified	19
Total	212

*From Bosher et al., Surg 45:91, 1959.

TABLE 3
Multiple Arteriovenous Fistulae*

Number of fistulae	Number of cases
2	30
3	7
4	7
5	2
6	1
7	2
"multiple"	23
Not specified	45
Total	117

*From Bosher et al., Surg 45:91, 1959.

In Table 4 the multiple lesions are grouped according to their regional location. Fifty are unilateral and 50 bilateral; 17 cases were not adequately specified.

TABLE 4
Location of Multiple Arteriovenous Fistulae*

Unilateral		50	Bilateral		50
Same lobe	22		2 lobes	25	
Left upper	5		3 lobes	15	
Left lower	5		4 lobes	5	
Right upper	2		5 lobes	5	
Right middle	3				
Right lower	7				
Two lobes	20				
Three lobes	8				
Not specified		17			

*From Bosher et al., Surg 45:91, 1959.

In Table 5 the results of angiography of the 135 patients of the 328 who underwent that study are presented.

TABLE 5
Angiography*

Confirmed x-ray findings	108
Located additional arteriovenous fistula	11
Diagnostic with negative x-ray	9
Failed to show arteriovenous fistula	7
Total	135

*From Bosher et al., Surg 45:91, 1959.

In 20 cases arteriovenous fistulae were identified by angiography when they were not visible on the conventional plain film. It is probable that some of the previously mentioned "unilateral" cases are in reality examples of bilateral arteriovenous fistulae which remained unproved because angiography was not employed. Furthermore, a number of unsuspected cases have been found at operation.[9] It is clear that a large arteriovenous fistula does not rule out the presence of other small, inconspicuous fistulae in the same or opposite lung.

Signs and Symptoms

Clinical symptomatology generally becomes manifest in the third decade of life but may occur at an earlier age. In the 140 patients whose records were reviewed by Stringer et al.,[3] 25 to 30 per cent had symptoms from early childhood. Cyanosis is often the first sign to appear, followed by digital clubbing. Both the cyanosis and the clubbing reflect the accompanying arterial oxygen unsaturation. Epistaxis, hematuria, hematemesis or bleeding lips are often the presenting complaints in patients with accompanying telangiectasia. In each instance the size of the lesion determines the severity and, in turn, the age of symptomatic onset. Weakness, dizziness, numbness, faintness, diplopia, thick speech and chest pain probably reflect the associated anoxia and polycythemia.[14]

A murmur is commonly heard over the fistula. It is usually continuous, with maximal intensity in late systole and early diastole. The murmur is generally loudest on deep inspiration and barely audible on subsequent ex-

piration; however, these findings are variable. Sometimes the bruit is audible only over the precordium; in other instances no murmur can be heard at all.[16] One patient had a purely diastolic bruit of increased intensity on deep inspiration.[6]

Blood Volume

Blood volumes have ranged from normal to extremely high values (4,800 to 12,900 cc). Hematocrit levels have been reported from 40 to 84 per cent. The usual hematocrit value is between 60 and 75 per cent.[6]

Physiologic Data

Cardiac Catheterization Studies

By using cardiac catheterization techniques, pressures, oxygen content and saturation, cardiac output and degree of shunt may be calculated and the lesion may be demonstrated by angiography.

Although pulmonary hypertension might be anticipated, it is usually not found with pulmonary arteriovenous fistula. Cardiac catheterization reveals essentially normal pressures in the chambers of the right side of the heart and its tributaries. Systemic blood pressures and pulmonary artery pressures are also normal.[6,16]

Arterial oxygen saturation ranges from 50 to 90 per cent.[3,6] In those patients studied postoperatively in whom a good result was obtained the arterial oxygen saturations returned to normal levels. Preoperatively, breathing 100 per cent oxygen for as long as one-half hour did not correct the unsaturation.[16]

Pathophysiology

The physiologic abnormalities are caused by the shunting of blood from the pulmonary artery to the pulmonary veins (right-to-left shunt).[17,18,19] These changes are similar to those encountered in an area of atelectasis which is in effect a pulmonary arteriovenous shunt, since blood passes through the lungs for gaseous exchange. Arterial oxygen unsaturation and ultimate cyanosis ensue.

Polycythemia

Hypoxemia stimulates erythropoiesis and ultimate compensatory polycythemia.[20,21,22] The reticulocyte count is frequently elevated and blood volume excesses result from the increased erythropoietic activity. The increase in blood volume is mainly cellular, whereas the plasma volume tends to remain at or near normal levels.[6] However, the chronic hypoxemia does not permanently modify the activity of the erythron. In those patients in whom corrective surgery was performed the hematologic studies returned to normal within several weeks.[3,6,9]

Absence of Cardiac Hypertrophy

The absence of cardiac enlargement was noted by most investigators. In contrast, an increase in heart size as well as cardiac output and blood volume is frequently encountered in patients with peripheral arteriovenous fistulae. The lack of cardiac hypertrophy and the absence of pulmonary hypertension in patients with pulmonary arteriovenous fistulae may be related to the lower pressures normally found in the pulmonary circulation.[6,16]

Differential Diagnosis

Polycythemia

More than half of the reported patients with pulmonary arteriovenous fistulae have evidences of polycythemia.[3,6,19,16] In spite of high hematocrits and red blood cell counts, the white blood count is usually within normal limits. This finding is helpful in differentiating primary polycythemia vera. In addition, oxygen saturation is generally normal in polycythemia vera in contrast to the decreased saturation usually found with pulmonary arteriovenous fistulae associated with secondary polycythemia.

X-ray studies, including angiocardiography, are the most useful diagnostic aids. The continuous murmur heard in patent ductus arteriosus may cause diagnostic confusion, but cardiac catheterization will generally differentiate between these two clinical entities.

Pulmonary Arteriosclerosis

Primary pulmonary arteriosclerosis may also be confused with pulmonary arteriovenous fistulae. The most prominent manifestation in these subjects is dyspnea which may be accompanied by cough, dizziness, syncope, chest pain and hemoptysis. In addition, repeated episodes of atelectasis or infarction often occur. The latter findings are especially apt to be confused with the dense shadows of pulmonary arteriovenous fistulae. In primary pulmonary hypertension, however, right ventricular hypertrophy is noted on the electrocardiographic tracings, and cardiac catheterization reveals pulmonary hypertension (in contrast to the normal pulmonary artery pressures found in patients with pulmonary arteriovenous fistulae).

Intrathoracic Masses

Tuberculosis, fungus infections, bronchogenic carcinoma, and other intrathoracic mass lesions must also be considered in the differential diagnosis.

Roentgenologic Considerations

The x-ray findings encountered in patients with pulmonary arteriovenous fistulae depend primarily upon the size of the arteriovenous shunt. The anatomic location is also important since other nearby densities may obscure the smaller vascular lesions. Most fistulae occur in the lower lobes. Not infrequently two or more lesions are present.[3,9]

Pulsation of the tumors may be seen fluoroscopically, and variations in size may be observed coincident with changes in intrathoracic pressure. The fistulae tend to become smaller with Valsalva maneuver (deep inspiration followed by forced expiration against the closed glottis), whereas Mueller's test (deep expiration followed by forced inspiration against the closed glottis) causes an increase in the size of the mass.[10,23] These variations, however, may be subtle and difficult to observe. The presence of transmitted pulsations may also obscure the diagnosis, especially when the tumor is located near the hilum. Lindgren[23] has stressed the importance of careful study of the pulmonary vessels and their relationship to the pulmonary tumor. He believes the latter observations provide the most reliable criteria for making a correct roentgenographic diagnosis. Even small arteriovenous fistulae possess at least two vessels connecting with the hilar vasculature. The pulsation of peripherally located lesions can often be best demonstrated by appropriate kymographic studies.

Pulmonary arteriovenous fistulae usually present roentgenographically as rounded, coin-like lesions located in the lower lobes of the lung.[6,23] Com-

municating afferent and efferent vessels are often visible on the routine chest films, but calcification is not commonly seen.[23] The cardiac silhouette is generally normal. This contrasts with the usual findings in peripheral arteriovenous fistulae and congenital heart disease in which cardiac enlargement is commonly observed.

Special roentgenographic studies offer additional diagnostic aid. Laminography[6,23] may visualize the communicating afferent and efferent vessels more precisely and may also define the location of the lesions more accurately. Angiocardiography usually confirms the vascular nature of the lesions and outlines their connections with the pulmonary artery and veins. This technique may also demonstrate other lesions which are not observed on routine chest films.[3,6,9,23] Special caution should be exercised with the use of angiocardiography since the increase in red cell mass associated with this disease increases the possibility of intravascular thrombosis.[6] Angiocardiography is the most accurate means for making the diagnosis and should be performed before therapy.

Treatment

Since the first pneumonectomy performed for pulmonary arteriovenous fistula in 1940, there has been a trend toward conservatism in the surgical resection of these lesions. Janes[24] in 1941 and 1942 carried out bilateral local excisions. Whittaker[25] in 1944 resected a lobe for this disease, but the patient died postoperatively. Blalock[3] apparently performed the first segmental resection for this disease. Since there are numerous cases of multiple fistulae, and new lesions occur in previously studied patients, it is important to conserve as much functioning lung tissue as possible. The best technique is to isolate the lesion and to resect it in a bloodless field. From the literature a total of 239 cases operated upon resulted in 13 operative deaths.[9] Table 6 shows the results of that series.

TABLE 6

Results of Surgical Treatment*	
Cured	173
Improved	19
Unchanged	2
Operative death	13
No information	32
Total	239

*From Bosher et al., Surg 45:91, 1959.

The indication for surgical therapy is clear in cases with increasing cyanosis, hemoptysis or alarming nervous symptoms. Patients with minimal symptoms run the risk of rupture,[22,26,27] cerebral embolism,[23] and cerebral abcess.[28,29,30] Intervention in these cases will depend on localization, the number of fistulae and the age of the patient. Delaying resection for any but the most minimal of cases seems less advisable in these days of better surgical and anesthetic techniques.

Summary

Pulmonary arteriovenous fistula is an abnormal communication between the pulmonary artery and vein, resulting in a right-to-left shunt. The patient presents with cyanosis, clubbing, dyspnea, and variable neurologic complaints.

Unsaturation of arterial oxygen and polycythemia are characteristic. Diagnosis is clarified by plain chest films, electrocardiogram, and cardiac catheterization with angiocardiography. Treatment is appropriate surgical resection, if possible.

References may be secured from the Grand Rounds Editor.

Rietti-Greppi-Micheli Syndrome

This form of hemolytic icterus with decreased red cell fragility belongs in the category of Mediterranean hemolytic syndromes of moderate degree. It is a heredofamilial constitutional disorder that has been observed most frequently in Italians but also in other residents of the nothern Mediterranean coast. Scattered cases, occurring perhaps through heredity and migration, have been reported in various parts of the world.

Erythrocytes are elliptoid, exhibit poikilocytosis, and show increased osmotic resistance to hemolysis and decreased red cell fragility. The intense erythrocytic disintegration is accompanied by signs of increased mechanical fragility. According to Marmont and Bianci, pathologically increased mechanical fragility occurs only in iron-deficient anemias.

The pathologic process varies from a barely perceptible abnormality of the red blood cells to a severe degree of anemia, icterus, and splenomegaly. It resembles or at least has many analogous features of Cooley's anemia; however, variations in the clinical pattern and characteristics make it difficult to classify these cases.

The pathogenesis of the syndrome is speculative. A congenital error of iron metabolism is suspected, involving perhaps faulty stromatohemoglobin bindings. This deficiency is sometimes described as metabolic dyserythropoesis. Although the course is benign, therapy is difficult. As a rule these patients are iron resistant, even to iron given by the intravenous route.

Durham, Robert H.—Encyclopedia of Medical Syndrome
Hoeber Medical Division, Harper and Row, New York

IT'S THE LAW

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An insured individual, whose foot was amputated as the result of injury sustained in an accident, was not entitled to recover the benefits provided in his accident insurance policy for the loss of the foot, because the loss did not occur within 90 days of the accident. The insurance policy stated very clearly that the coverage was limited to cases where the foot was actually amputated within 90 days of the accident.

Cornellier v. American Casualty Company, 389 F .2d 641 (C.A. 2, January 19, 1968). The Citation 17:4, June 1, 1968.

The true believer is in a high degree protected against the danger of certain neurotic afflictions; by accepting the universal neurosis he is spared the task of forming a personal neurosis.—Sigmund Freud

---

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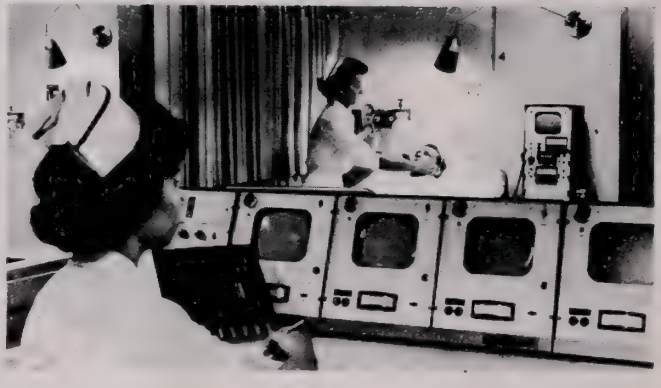
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Abstracts, Briefs and Commentaries

A FIVE-YEAR HISTORY OF THE MINNESOTA RESIDENTIAL TREATMENT CENTER

The Minnesota Residential Treatment facility is a service arm of the Minnesota Department of Public Welfare which provides psychiatric treatment services for sixty-four mentally ill children. Since July of 1967 the admission policy has been strictly limited to the acceptance of children under twelve years of age. Prior to this date (and this will be reflected in the statistics which will follow) adolescents were accepted at the Treatment Center. Admissions are processed through the appropriate county welfare departments. Initial diagnosis and evaluation studies to determine the needs for residential treatment are carried out by community mental health centers, child psychiatric centers, or by child psychiatrists in private practice. If a child is accepted for treatment, the welfare department of his county pays ten percent of the actual cost of his care and the parents pay the rest, according to their ability, as determined by the county welfare department (in most cases a token amount or nothing at all).

There have been a total of 91 admissions to the facility for the period of June 1963 through December 1967. The ratio of boys to girls admitted to the facility has been approximately two to one, with 59 boys admitted and 32 girls. Other centers report a higher ratio of boys to girls of three to one and four to one. The youngest child admitted to the facility during this time was a five-year, one-month-old boy; the oldest youngster at the time of admission was an adolescent male seventeen years of age. It should be noted that this boy was a member of the first group of youngsters admitted to the facility and remained at the Center for only two months. The average age on admission was twelve years, nine-and-a-half months, and the typical duration of residential care was two years, two and one-third months.

Behavior which comes directly under the scrutiny of the community, such as truancy, social maladjustments, stealing, running away, fighting and temper outbursts, and suicidal attempts, was clearly associated with a significant number of admissions to the center.

A total of 58 children were returned home, eleven to foster homes and eight to other placements such as group living facilities. Therefore 77 children were returned to a community setting, and only 14 required institutional

care. The inescapable conclusion is that the Center has served an important treatment role in terms of resolving the serious psychopathology of these children and in facilitating their eventual return to the community.

There are still voices which can be heard saying that there is no need for residential care and that all children's problems can and should be dealt with in the community. One certainly cannot quarrel with this as an ideal point of view; but unfortunately neither the community nor society in general has achieved such a degree of sophistication and understanding that it is in a position to care for those children who eventually find their way to a residential treatment center. It is evident that when this stage is reached, the family, the school, and the community have literally excluded the child as unacceptable. It is the responsibility of the institution to insist, however, that all these areas continue to be involved in the ongoing care and treatment of the child and to work diligently toward providing a suitable environment for his return to the community.

The residential treatment of children is only now beginning to attract the attention and interest of a society increasingly concerned about the emotional health of its children. We expect that the Minnesota Residential Treatment Center will be in the forefront both in terms of experience and treatment of the emotionally disturbed child in residence.

John C. Duffy, M.D.
Minneapolis, Minnesota

EMOTIONS

The limbic area of the brain is the emotional portion where the basic feelings of anger, fear, pleasure, sadness, joy, sociability and sexuality arise. It is known that some people suffer from impulsive sporadic attacks of uncontrollable rage which might lead to homicidal activity.

In the animal the limbic brain has been extensively explored and experiments have shown that electrode stimulation can stop a bull in mid charge or cause a cat to park on a button which delivers constant gratifying shocks to limbic regions. In this manner the electrodes locate troublesome neural tissue which can then be carefully removed.

In the epileptic it is thought that there might be seizure areas in the lower half of the limbic rings, and it is speculated that individuals prone to periodic violence could be victims of focal brain damage resulting from years of bruising emotional trauma.

It has been further suggested that there may be a critical time when the brain learns social behavior.

Carl O. Rice, M.D.
Minneapolis, Minnesota

Emotional Brain, Patricia McBroom, Sci News, 94:91, 1968.

ANGIOLOGY

Leg claudication distance can be accurately measured by treadmill. One hundred and fifty-five patients after recording their claimed claudication distance had walking distance measured repetitively on a slow treadmill. The distance was measured as "relative claudication distance" (i.e., when pain begins) and the "absolute claudication distance" (i.e., pain forces patient

to stop).

There was no correlation between the subjective claudication distance and the measured relative or absolute claudication distance.

Claudication distance is affected by motivation, speed and incline of walking, drugs (including placebos) and training.

It was concluded that subjective claudication distance is not a quantitative measure that accurately indicates the stage of vascular disease of the legs.

Jerome T. Grismer, M.D.
Minneapolis, Minnesota

J. Siggaard Andersen, M.D., F. B. Peterson, M.D.: Angiology 19:426, 1968.

MEDICAL RESEARCH GROUP DEVELOPS ELECTRONIC PROGRAM FOR CONTROL OF TUBERCULOSIS AND OTHER CHRONIC DISEASES

The Medical College of Georgia and the National Cash Register Company together have developed a computerized system for monitoring and analyzing the incidence of tuberculosis and other communicable diseases within a given state or smaller community. The system is the product of two man-years of programming effort.

Under a manual system the scheduling of tests and examinations is ordinarily a tedious operation requiring the attention of a medically competent individual, usually a doctor or a nurse. A TB nurse may spend 20 percent of her time reviewing records.

Under this electronic system the computer can review and update 500 patient records—including the preparation of schedules and the writing of the appointment letters and reports on the 500 patients—all within 12 minutes. The system frees the doctor or nurse for more demanding medical functions. Furthermore, the computer applies a rigid set of criteria to produce consistent results under all conditions.

Editor's Note: Computerized medicine is, for the moment confusing, but it's on the way.

RESECTION OF DESCENDING THORACIC ANEURYSMS WITHOUT LEFT HEART BYPASS

Resections of aneurysms of the descending aorta require preliminary interruption of flow by cross-lamping. Ischemic injury to the spinal cord, kidneys, distal organs and acute left heart failure result if flow is not established. Various techniques (left atrial-femoral bypass, femoral vein-femoral artery bypass, or external shunts) have had problems of flow, heart failure, clotting or excessive bleeding from heparinization.

Two types of external shunts (7.5 mm. cannulas and three-eighths inch tubing; 9 mm. cannulas and one-half inch tubing) are placed into the proximal and distal aorta. No heparin is given. This procedure is especially suitable in acute traumatic aorta rupture and false aneurysms. Eleven patients were successfully operated and aneurysms removed without complications.

Jerome T. Grismer, M.D.
Minneapolis, Minnesota

D. R. Kahn, M.D., S. Vathayanon, M.D., H. Sloan, M.D.: Resection of Descending Thoracic Aneurysms Without Left Heart Bypass. Arch Surg 97:336, 1968.

IRRADIATION TREATMENT FOR PEPTIC ULCER

X-ray irradiation of the stomach in the treatment of peptic ulcer was first suggested in 1909, and by 1935 over 200 papers had been published on this treatment. Careful studies on thousands of patients have established that irradiation reduced the recurrence rate to one fifth and hastened healing. Nevertheless, this use of irradiation is not generally known and has not been widely adopted. Many prefer surgery despite its risks and the dumping syndrome it often produces.

The technique of irradiation is simple: the stomach is outlined with barium and the skin marked during fluoroscopy. An anterior and posterior field is centered over the upper two thirds of the stomach (where the acid-secreting cells are). An irradiation dose of 2000 r is given through each port in six to eight treatments. In most institutions the 250-kv. apparatus is used.

Results are reported in 121 patients with complicated peptic ulcer, 79 of whom have been followed up for over four years, after cobalt 60 teletherapy. The reactions were minimal.

A total of 629 gastric secretion studies were done. In 90 percent of the patients the basal gastric secretion was reduced more than 50 percent in the first six months, though hyperacidity usually recurred after six months to one year. In 87 cases the ulcer did not recur; in 13 there was a questionable recurrence and in 21 a definite recurrence.

Cobalt 60 teletherapy is a very useful method of treating peptic ulcer, especially in cases where cardiac lesions, hypertension or other complications contraindicate surgery.

Courtesy of World-Wide Abstracts

Brown, C.: American J Gastroenterology 38:3:278.

THE PARTIALLY SEVERED ARTERY

The incompletely severed artery, unable to retract or constrict, may result in exsanguination, recurrent hemorrhage, arteriovenous fistula or false aneurysm. Fifty-seven patients, selected because of injuries to major arteries of head or extremities, presented with clinical shock (23%), large hematomas that may pulsate (65%), diminished pulses (30% of those recorded) and bruits (53%). Peripheral arteriography demonstrated abnormalities of extravasation, occlusion, arterial defects, arteriovenous fistula or false aneurysm.

Emphasized is the presence of normal or diminished pulses despite partial severance.

Surgical exploration and repair is possible in most patients, i.e., 50 of the 57 patients presented.

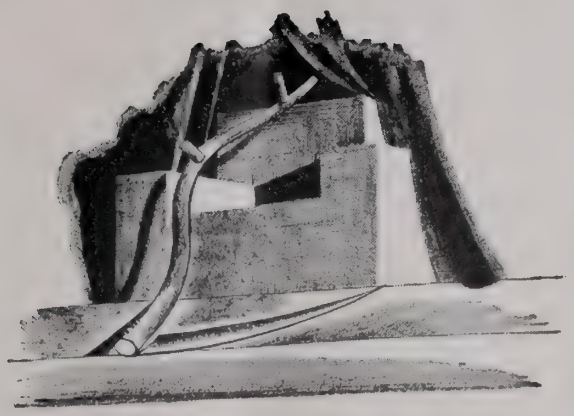
Jerome T. Grismer, M.D.
Minneapolis, Minnesota

J. D. Saletta, M.D., R. J. Freeark, M.D.: The Partially Severed Artery. Arch Surg 97:198, 1968.

DERIVATIVELY SPEAKING

Cirrhosis—from Greek *kirrhos* (orange-yellow).

Every man is a damn fool for at least five minutes every day; wisdom consists in not exceeding the limit.—Elbert Hubbard



In Memoriam

For death betimes is comfort, not dismay,
And who can rightly die needs no delay.

—Petrarch

CLAUDE F. DIXON, M.D.

Dr. Claude F. Dixon, 75, retired Mayo Clinic surgeon, died September 11. He specialized in abdominal surgery and joined the Mayo staff in 1929. After a 29-year career, Dr. Dixon retired in 1957.

He was a native of Piedmont, Kansas, and received his medical degree from the University of Kansas. He attended the Mayor Graduate School in Rochester and was first assistant for two years to the late Dr. Charles Mayo before joining the clinic staff.

Dr. Dixon was a member of the Zumbro Valley Medical Society and the American Medical Association and was a Life Member of the Minnesota State Medical Association. He is survived by his wife and a daughter.

JOSEPH A. POIRIER, M.D.

Dr. Joseph A. Poirier, 88, retired Forest Lake surgeon, died October 9. He was born in Appleton and graduated from Hamline Medical College in 1903.

He started practicing in Forest Lake in 1903 and practiced there until his retirement in 1954.

Dr. Poirier was a member of the Washington County Medical Society and the American Medical Association; was a 50 Club and Life Member of the Minnesota State Medical Association; and served as Forest Lake health officer.

He is survived by his daughter and a son.

WILLIAM D. CLEAVES, M.D.

Dr. William D. Cleaves, 52, Sauk Centre physician, died October 21, of injuries sustained in an automobile accident. He was a graduate of the college of St. Thomas, St. Paul, and of the University of Minnesota Medical School. He had practiced in Sauk Centre from 1946 until the time of his death.

He was a member of the Stearns-Benton County Medical Society, the American Medical Association and the Minnesota State Medical Association.

Dr. Cleaves is survived by his wife, one daughter and two sons.

JOHN A. LEPAK, M.D.

Dr. John A. Lepak, 81, St. Paul physician, died September 28. Born in Gnesen, Minnesota, Dr. Lepak had lived and practiced medicine in St. Paul for fifty years.

He was on the medical staffs of Ancker, St. Luke's, St. Joseph and Charles T. Miller hospitals and held memberships in the Ramsey County Medical Society, St. Paul Society of Internal Medicine, Minnesota Pathological Society, Minnesota Academy of Sciences, Minnesota Academy of Medicine, American Medical Association, American Society of Geriatrics, American Society of Endocrinology and a life fellowship in the American College of Physicians. He was a life and 50 Club Member of the Minnesota State Medical Association.

He is survived by his wife and three sons. Dr. Lepak has two brothers practicing medicine in Duluth, another brother practicing medicine in Oak Park, Illinois and a fourth brother practicing in Oak Lawn, Illinois.


Knee-deep

in osteoarthritic pain

If aspirin doesn't help, move in with Tandearil.

The trial period is brief: 1 week. Try one tablet q.i.d. at first. Tandearil usually starts working within 3 to 4 days. When response occurs, as little as 1 or 2 tablets daily may hold back pain and stiffness, and increase joint motion.

On the next page is a summary of adverse reactions, contraindications, warning and precautions.

Tandearil.
It can help get his mind off his knee.

Please review full Prescribing Information carefully before prescribing.

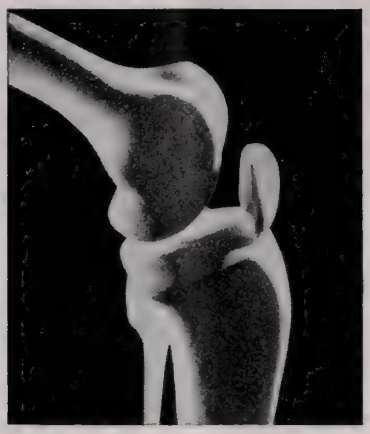
For osteoarthritic knees, spines, shoulders, hips, etc.:

Tandearil®
oxyphenbutazone

Tandearil, oxyphenbutazone:
For brief summary see next page.

Geigy

TA-6006



Tandearil®
oxyphenbutazone

Contraindications: Edema; danger of cardiac decompensation; history or symptoms of peptic ulcer; renal, hepatic or cardiac damage; history of drug allergy; history of blood dyscrasia. The drug should not be given when the patient is senile or when other potent drugs are given concurrently.

Warning: This drug is an analog of phenylbutazone; sensitive patients may be cross-reactive. If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Instances of severe bleeding have occurred. Persistent or severe dyspepsia may indicate peptic ulcer; perform upper gastrointestinal x-ray diagnostic tests if drug is continued. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy. Use with caution in the first trimester of pregnancy, and in patients with thyroid disease.

Precautions: Before prescribing, carefully select patients, avoiding those responsive to routine measures as well as contraindicated patients. Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patients should not exceed recommended dosage, should be closely supervised and should be warned to discontinue the drug and report immediately if fever, sore throat, or mouth lesions (symptoms of blood dyscrasia), sudden weight gain (water retention), skin reactions, black or tarry stools or other evidence of intestinal hemorrhage occur. Make complete blood counts at weekly intervals during early therapy and at 2-week intervals thereafter. Discontinue the drug immediately and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.

Adverse Reactions: The more common are nausea and edema. Swelling of the ankles or face may be minimized by withholding dietary salt, reduction in dosage or use of diuretics. In elderly patients and in those with hypertension, the drug should be discontinued with the appearance of edema. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. The patient should be instructed to take doses immediately after meals or with milk to minimize gastric upset. Drug rash occasionally occurs. If it does, promptly discontinue the drug. Agranulocytosis, exfoliative dermatitis, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), or a generalized allergic reaction similar to a serum sickness syndrome may occur and require permanent withdrawal of medication. Agranulocytosis can occur suddenly in spite of regular, repeated normal white counts. Stomatitis, salivary gland enlargement, vomiting, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported. While not definitely attributable to the drug, a causal relationship cannot be excluded. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, hypersensitivity angiitis, pericarditis and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.

Dosage in Osteoarthritis: Initial: 3 to 6 tablets daily in divided doses. Usually unnecessary to exceed 4 tablets daily. A trial period of one week is considered adequate to determine the therapeutic effect of the drug. Maintenance: Effective level often achieved with 1 or 2 tablets daily, should not exceed 4 tablets daily.

In selecting appropriate dosage in any specific case, consideration should be given to the patient's weight, general health, age and any other factors influencing drug response.

Availability: Tan, round, sugar-coated tablets of 100 mg. in bottles of 100 and 1000.

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The Physician's Workshop

Pulmonary Function Tests*

Their Laboratory Value

UNTIL RECENTLY respiratory physiology has been the concern of a small number of men in large teaching centers; however, technical refinements and commercialization of instruments have now made pulmonary testing available to smaller centers. The clinician can develop a reasonable approximation of pulmonary function with physical examination, chest x-ray and perhaps fluoroscopy if he repeatedly compares his findings to those of the physiology laboratory. However, good correlation occurs only if the pathophysiologic state is well developed. The laboratory appears then to be the most efficient way of discovering the early or mild case and is the most exact way of evaluating the already well developed pathophysiologic state.

Clinical Signs

A well known modern textbook[5] of pulmonary diseases states: "The patient's response to exercise either walking on level ground or climbing stairs is a rough but reliable index of cardiopulmonary function." Many pulmonary physicians and surgeons agree with the statement to the extent that they feel they can evaluate pulmonary function on this basis without resorting to laboratory testing.

Dyspnea

A recent important study[12] showed that the absence of dyspnea on ascending a flight of stairs *by no means* implied the absence of pulmonary insufficiency (Tables 1, 2, 3). Pulmonary testing is seen to be the most reliable method of discerning the presence or absence of pulmonary disease and of assessing functional status.

Dyspnea, though variously described, is generally considered to be a subjective sensation of need for increased ventilation.[2] The primary function of the lung is to oxygenate and to remove waste products.[2,3] The etiologic factors which can interfere with this primary function are many (Table 4), and clinical separation is often difficult. Function testing using the battery of spirometry, N_2 washout and arterial gas studies, however, will often point to the correct diagnosis.

Cyanosis

The presence of cyanosis may lead the physician to suspect inadequate ventilation. The detection of cyanosis, however, is notoriously difficult; in fact severe pulmonary insufficiency may exist without cyanosis, while in polycy-

TABLE 1*

Shortness of Breath on Climbing One Flight of Stairs in Relation to Ventilatory Findings

Ventilatory Defect	Total Number of Patients	Short of Breath	
		Yes	No
Normal	40	25	15
Restrictive	29	19	10
Obstructive	57	42	15
Combined	74	62	12

*From Lerner et al. Amer Rev Resp Dis 92:822, 1965 with permission.

TABLE 2*

Distribution of Age in Relation to Abnormal Ventilatory Findings and Shortness of Breath on Climbing One Flight of Stairs

Age	Total Number of Patients	Short of Breath			
		Yes		No	
		Normal	Abnormal	Normal	Abnormal
20-29	7	2	2	3	0
30-39	29	5	16	4	4
40-49	56	8	34	5	9
50-59	36	6	24	1	5
60-69	50	3	32	2	13
70-79	22	1	15	0	6

*From Lerner et al. Amer Rev Resp Dis 92:822, 1965 with permission.

*Supported in part by the Ramsey County Foundation for Medical Education and Research.

themia severe cyanosis may occur without pulmonary insufficiency.[3]

Laboratory

Arterial blood gas studies are not essential when cyanosis is obvious; but when doubtful, arterial puncture is certainly warranted.[8]

Oxygen Saturation Determination

Oxygen saturation determination is also difficult and at best does not compare in sensitivity with arterial oxygen tension as an indicator of hypoxia.[15] The reason for this lack of sensitivity is the unique shape of the curve of oxyhemoglobin dissociation (Figure).

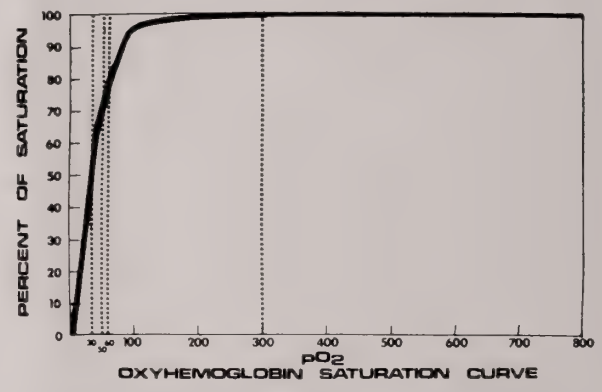
Oxygen Tension

A low PO_2 in patients with cardiopulmonary disease is likely due to one of the following:

1. If it is combined with an elevated carbon dioxide tension, hypoventilation is the cause.
2. In situations where uneven ventilation perfusion ratios occur in different areas of the lungs, the resultant venous admixture causes the hypoxia. The carbon dioxide tension may be low, normal, or elevated depending on the ability of the lungs to compensate.
3. Venous to arterial shunts are recognized by having the patient breathe 100% oxygen. If at this time the carbon dioxide tension exceeds 550 mm. Hg any significant anatomic shunt can be excluded.[18]
4. In diffusion abnormalities there is usually a drop in the carbon dioxide tension on exercise. However, a definite diagnosis of diffusion abnormality requires a special test called a diffusing capacity.

Carbon Dioxide Tension

Respiratory failure is generally diagnosed when the carbon dioxide tension is greater than 55 mm. Hg and the oxygen tension is less than 55.[18] Respiratory acidosis usually accompanies respiratory failure. It may be acute or chronic, compensated or uncompensated. It is not only the carbon dioxide per se, but the actual pH abnormality produced which can be harmful to the patient. Therefore, in order



Figure—Oxyhemoglobin saturation curve extended to conform to a pO_2 800. At physiologic levels (pO_2 100) the pO_2 is a more sensitive indicator of hypoxemia than O_2 saturation. This sensitivity is accentuated by the inhalation of enriched O_2 mixtures, i.e., a change in pO of 200 mm results in a change of only 3 percentiles of O_2 saturation. Above pO_2 of 300 there is no change in the already fully saturated hemoglobin while pO_2 increases proportionally to the mixture of O_2 inhaled. (Normal individuals achieve a pO_2 of more than 550 while breathing 100% O_2.)

TABLE 3*

Mean Values for Various Ventilatory Data in the Four Groups Paired as to "Yes" or "No" on Shortness of Breath Question

	Normal		Restrictive		Obstructive		Combined	
	Yes	No	Yes	No	Yes	No	Yes	No
FEV_1, liters	3.32	3.28	2.10	2.16	2.17	2.68	1.28	1.47
Per cent FEV_1	77.5	75.3	80.6	74.8	53.4	62.0	46.3	53 9
Per cent FVC, predicted	110.3	109.1	68.8	73.4	106.4	116 6	73.3	77.3
Peak flow, liters per minute	548.7	535.3	403.3	394.5	333.7	438.3	186.6	235 2
Percent peak flow, predicted	97.3	93.7	73.9	69.7	60.6	81.2	35.4	45.7

*From Lerner et al. Amer Rev Resp Dis 92:822, 1965 with permission.

to assess respiratory failure or respiratory acidosis, it is almost essential to know the pH, carbon dioxide tension and oxygen tension, and if possible the electrolyte status.[10,4]

Monitoring

Arterial gas studies are required to appraise the status of oxygenation, and these may also be used as a monitoring device in patients who are in respiratory failure.[4,18] Patients with considerable venous admixture, e.g., emphysema associated with pneumonia or severe interstitial fibrosis, often require 45-60% oxygen in inspired air to maintain an oxygen tension between 70-90 mm. Hg, while patients with emphysema and bronchitis alone usually reach these tensions by breathing 30-40% oxygen.[13] Oxygen delivery systems such as nasal and oropharyngeal catheters, nasal prongs, loose masks, and body tents provide only 30-50% oxygen.

Thus, unless monitoring is employed in such cases, an inadequate delivery system may not be recognized. Occasionally the administration of supplemental oxygen decreases the respiratory drive to the point where ventilation is insufficient. Unless the patient is monitored carefully with arterial gas studies, this condition may become apparent only after carbon dioxide narcosis has supervened. In closed systems where the patient is being ventilated through a cuffed endotracheal tube, frequent arterial gas studies are necessary to insure that proper ventilation is being dispensed in order to be able to compensate for the rapid changes in carbon dioxide tension and pH which may occur.

Surgical Risk

Fortunately the chance of a patient developing a respiratory complication during surgery is now less common because of recent refinements in surgical and anesthesia techniques. Filley[8] points out that bad-risk patients with known severe pulmonary disease often do better than patients whose moderately reduced function is unrecognized. The reason for this is that the former patients are watched closely and given intense care while the latter may receive only routine care. It has been recently shown that patients who have abdominal surgery, particularly where large segments of peritoneum have been injured, have remarkably high oxygen requirements. Individuals with only a moderate decrease in ventilatory ability (smokers and bronchitics) who are not usually tested may fail to have their metabolic oxygen needs satisfied in the postoperative state

TABLE 4

Organic Factors Conducive to Dyspnea

I Increased respiratory muscular work.
  1. Central hyperventilation—metabolic acidosis.
  2. Increased ventilatory requirements.
    (a) inadequate O_2 delivery: arterial hypoxemia from high altitude
      anemia
      cardiac failure
    (b) exercise

II Altered physical properties of lung.
  1. Increased elastic work of lung: pneumonia, atelectasis, pleural fluid pneumothorax
  2. Increased elastic work of chest wall: kyphoscoliosis, rheumatoid spondylitis, obesity
  3. Obstruction to air flow: emphysema, bronchitis, asthma, tumors, etc.

III Decreased muscular ability to do work.
  1. Muscular diseases: myasthenia, polio, Guillain-Barre syndrome.
  2. Reduced mechanical advantage of muscle due to:
    (a) marked inspiratory position—emphysema.
    (b) marked expiratory position—obesity.

IV Hypoxia
  1. Hypoxic hypoxia
  2. Anemic hypoxia
  3. Circulatory hypoxia
  4. Histotoxic hypoxia

V Psychogenic

with equally disastrous results.

Postoperative Complications

The majority of postoperative complications, pneumonia and atelectasis, occur in those individuals with obstructive lung disease.[11,13,14,15] Foreknowledge with preoperative pulmonary function tests and postoperative arterial gas studies would help to prevent these complications. Indeed, a pulmonary function screening procedure for all patients who are to undergo anesthesia has been recommended.[14,11] With the advent of the computer there might well be a practical screening procedure for pulmonary function in the future, as are chest x-ray and electrocardiogram at the present time.

Thoracic operations impose great changes on the respiratory system and in addition may superimpose a permanent ventilatory deficit unless the surgery is for correction of a specific mechanical problem. It has been stated by Gaensler that resection for infectious processes is contraindicated in patients with maximum voluntary ventilation of less than 50%, while the Mayo Clinic series suggests 35% as the lower limit.[14] Where cancer surgery is indicated, a pneumonectomy should not be done on any individual with a maximum voluntary ventilation of 55% or less who also does not respond to bronchodilator therapy. A lobectomy is safe on a patient with a maximum voluntary ventilation of greater than 40%.[14]

Disability evaluation is increasingly important—both because of the number of individuals affected with pulmonary disease and because of the demands on the financial resources of the community. It is the physician's job to make an evaluation of ability to work, to give a firm basis for judgment; and the only objective evidence we have thus far on which to make the decision are pulmonary tests.[14] On evaluating obstructive disease, studies of forced vital capacity, oxygen consumption and maximum voluntary ventilation are important criteria of disability, while in restrictive disease arterial blood gases are most necessary. Duplicate testing usually demonstrates malingering.

Conclusion

Although a comprehensive history and a meticulous, skillful examination will frequently uncover the presence or probability of complicating pulmonary disease, patients may be exposed to excessive risk unless baseline pulmonary laboratory studies are done preoperatively. Careful laboratory assessment of the dyspneic or hypoxemic patients is generally necessary to give an informed opinion. Intelligent respiratory therapy cannot be ordered without a knowledge of the arterial blood gas status. Pulmonary disability determination units require the objectivity of physiologic data as a baseline for decision. In short, the physician, the surgeon, and even the bureaucrat require pulmonary function tests for the adequate assessment and intelligent treatment of thoracic problems.

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St. Paul, Minnesota

Acknowledgment: Miss Catherine Baden, RN, and Sister Roland, OSB, for their kind help in preparation of this manuscript.

*Chief, Pulmonary Section, Department of Medicine, St. Paul Ramsey Hospital.

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10-18. May be secured from the author or the reprints.

Always do right; this will gratify some people and astonish the rest.—Mark Twain

Coronary Care Unit

Model of Medical Organization

WHILE LISTENING to a paper at the Minnesota Society of Internal Medicine on May 18, 1968, presenting the experiences of the Coronary Care Unit at Mount Sinai Hospital in Minneapolis, the manifold implications of this type of unit struck me so forcibly that I decided to write them down. Since I have no personal stake in these units at the moment, I fancy that I am able to perceive the implications with a detached and objective view not possible for those engaged in their planning. Not being involved, I am like a man standing atop a six-story building watching an elephant being washed in the parking lot below. The washers are the hospital administrator, the electrocardiographer, the family physician, the private health insurance provider, the nursing supervisor, the professor, the health care planner, and the patient; each wants to be sure his part of the elephant is clean but cannot view the entire result from his vantage point. This paper is written in the hope that the overview may be useful to the washers. I have a real stake in the outcome of their labors, for there is a great statistical likelihood that I and everyone who reads this paper may one day find ourselves bedded down in a coronary care unit and would appreciate all the effectiveness this new phenomenon is capable of because our lives may depend upon it.

Medical Value

I will ask the reader to accept, as I do, that a coronary care unit can be shown to save lives, compared to whatever care was given prior to the coronary care unit concept. My colleagues tell me that the real value of the unit is prevention of "electrical death," that is, prompt recognition and appropriate treatment of ventricular arrhythmias incompatible with survival. This means that every patient with a proved or suspected myocardial infarction must be monitored for three to seven days, during which time machines and trained personnel must be constantly available to recognize and treat threatening arrhythmias instantly. Once one accepts the premise that a predictable number of lives will be saved, one has no medically defensible position but to insist that the medical profession proceed as rapidly as possible to make this life-saving discipline available to every patient who needs it. There is no other scientific, moral or ethical position one can take regarding this matter.

Economic Implications

When we accept the fact that constructing and staffing coronary care units save "x" lives and cost "y" dollars, we have only to decide what the value of a life is. No small matter! We are told that the price of hospital care is rising alarmingly and rapidly and may soon reach $100 to $150 per day. It is precisely things like coronary care units that cause this increase in hospital care costs. New space must be built or old space renovated to fit new function. Hardware (telemetry equipment) must be purchased. Both nursing and physician staffs must be trained in the use of equipment, interpretation of the alarms it sends, and corrective measures to be applied instantaneously. The cost per monitored bed in a coronary care unit is about seventy-five dollars per day. Can the private insurance sector afford to absorb these costs? If not, will we find it necessary through taxation to underwrite these costs for each other, as a nation? Will the number of

lives saved provide the earning power to support the program? I presume actuarial and statistical methodology exists to answer these questions; but society, given adequate medical leadership, will really decide these questions for us.

Location

If coronary care units are to serve the public best, they must be located in the community hospital rather than in the remote reaches of the metropolitan, university type, referral care center. Acute myocardial infarction happens suddenly and often unexpectedly and must be cared for "in the field." It is a fact in Minnesota that community private hospitals care for the bulk of acute myocardial infarctions, rather than the teaching and research institutions like the University, the Mayo Clinic and the V.A. Hospital, which tend to be at the second echelon level removed by physical and organizational inaccessibility from the acute illness. Even if the second echelon referral centers created such units, we would have to carefully evaluate the possible dangers to the patient caused by separation in distance or in time from optimal early care.

How will the small community hospitals (forty-bed size) solve the problem of coronary care? The answer lies in organization and telemetry. These small hospitals will operate as satellites of a central monitoring station, borrowing medical and nursing skills by sending data and necessary instructions over ordinary telephone wires. They will also need ongoing training programs for doctors, nurses, and technicians, either by sending these people to the central monitor station periodically, or having central monitor hospital staff circulate through the satellites. The situation is analogous to a small company using a time-shared computer: through organization they enjoy computer advantages even though they could not efficiently utilize (or afford) a full-time computer.

Teaching Implications

Inasmuch as physicians are trained at medical school and related hospitals and acute myocardial infarctions are seen at the local community level, it becomes more difficult to teach the care of this disease to physicians in training. It seems likely the universities will have to rotate their trainees (at all professional levels) through the coronary care units of the community hospitals to get this experience. This will perforce involve the medical school more in the medical community, a situation which likely would benefit both parties. I assume the major contributions of the University to the partnership would be research methodology, quality control, and teaching skills, while the major contributions of the community hospital would be facilities, patients, and provision of the training program for nurses, technicians, physicians and allied health professionals. A new kind of professional, the "coronary care nurse," is being born from just that kind of union at present.

People Involved

The coronary care unit offers a new model of teamwork, in which the physician relinquishes some of his leadership role to the nurse. The team consists of a machine at the bedside, a central bank of monitors, a specially trained nurse to form the first human link with the machine, an anesthesiologist, an inhalation therapy technician, the cardiology resident and the director of the coronary care unit. There may be others I haven't named. Each person (or thing) on the team must know his job and integrate his function with that of the other team members to produce the desired result—saving the patient's life. They must train together, scrimmage together, fail together and succeed together. They must be available 24 hours a day, 365 days a year. Any weakness in the team could destroy its functional effectiveness.

Alteration of Traditional Roles

The coronary care model threatens to modify long established doctor-patient, doctor-doctor, and doctor-nurse relationships, and I suspect role modification is going to be most difficult for physicians to accept. When the family doctor admits an acute myocardial infarction now he effects certain surveillance and therapeutic procedures which usually result in recovery. If certain complications ensue he has time to call a consultant, the time-honored method of doctor-doctor teamwork. If the

complication is ventricular fibrillation, and if we assume it will go unrecognized outside of the coronary care unit, the patient may die before consultative help (or any other help) can be obtained.

Acceptance of the philosophy of coronary care units is acceptance of the fact that nobody can predict when the untoward electrical event may occur; therefore all such patients must be monitored. The family doctor must surrender some of the responsibility for care of his patient to "the team" mentioned above. It is doubtful that the team as a consultant can make him a useful member just because it is his patient. More threatening to traditional relationships, the team leader should be the director of the coronary care unit, a full-time cardiologist who may even be a full-time hospital employee. Thus the "hospital" becomes the consultant, and role modification is necessary bilaterally.

Planning Implications

We have already presumed that our threatening new model

1. has demonstrable and predictable medical value in saving lives,
2. will be very expensive,
3. must be located in the community hospital,
4. should have a teaching liaison with the medical school that is mutually useful,
5. introduces a whole new team approach to a dramatic medical event, involving health professionals at multiple levels, and
6. profoundly alters the traditional doctor-patient and doctor-doctor relationships.

It is obvious that any concept in health care which pervades so many areas requires planning. How many coronary care centers does a state need? Where should they be located relative to population and transportation implications? Who should pay for them and how? Who should train the necessary health professionals to staff them?

To answer these questions the cardiologists are going to have to tell us how many patients with chest pain will present for care next year. Whether every chest pain patient should be monitored in a coronary care unit. For how long? How many beds will be required? Where should they be located? The economists and social planners will have to tell us the best way to finance this care. The community hospitals are going to have to demonstrate that they *can* work together to avoid duplication of facilities and *can* work with the established teaching centers to provide the necessary trained staff.

We seem to be starting off in our usual independent, expensive, unplanned way of having hospitals and their staff compete to see who can build the "biggest and best" coronary care unit. Can we afford this expensive ego food? Can we really learn to work together—family doctors, teachers, hospitals, economists, social planners? Who will lead us?

Summary

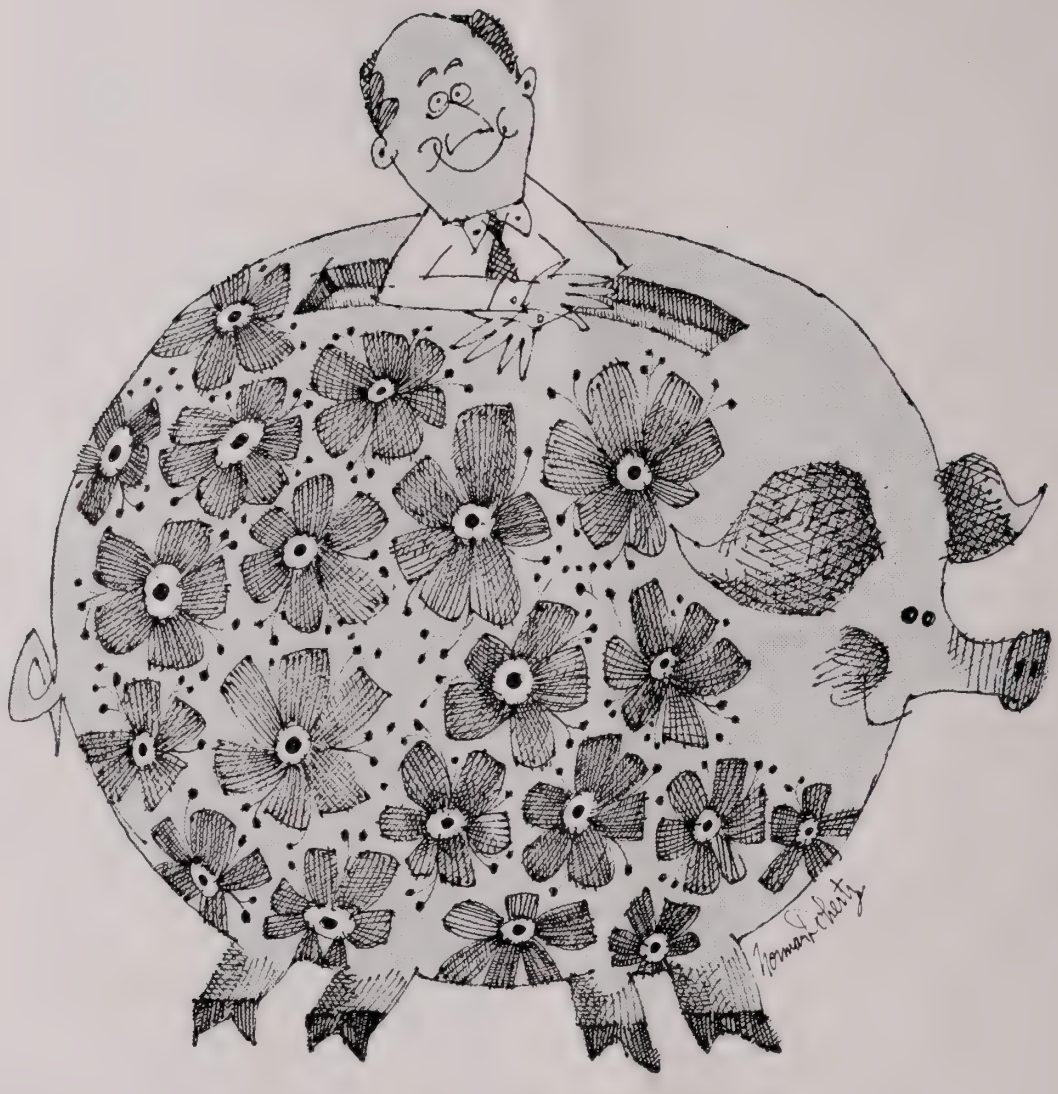
It is likely that many people who read these thoughts will have a chest pain some day. When that happens they will want the best care available because their life may be at stake. If accessability to a coronary care unit means the best care available, they will want to be in a coronary care unit.

As physicians we cannot accept any standard which provides less than optimal care, but at present only one or two percent of patients with acute coronary occlusion can enjoy the benefits of an adequate coronary care unit. We must therefore make available what we would like for ourselves to every person everywhere, insofar as it is within our power. The doctrine of one class of medical care for all is desirable as a basic human right. Society demands it and is willing to pay for it. It is our job to organize medical care along new lines every time the need arises. To do this we must subjugate our personal interests, "our own hospital's" interests and "our own medical school's" interests to the interests of our patients, wherever and whoever they may be.

The coronary care unit provides a delightful organizational challenge and, I suspect, is a prototype of many to come. We will have met that challenge if we can ensure that *every* person with chest pain receives the care we would choose for ourselves in a similar circumstance; and having met that challenge, we will be better physicians.

William R. Fifer, M.D.
Minneapolis, Minnesota

It is an infamy to die and not be missed.—Carlos Wilcox



The first thing to save for your old age is you!

Everyone dreams of a pleasant retirement. And practical people save for it. But what good are plans and dreams if you aren't around to enjoy them? Be smart and have a complete health checkup every year. 1,400,000 people living today are cured of cancer. And a yearly checkup could save many thousands more. Plan now to have a future. Make an appointment today for your health checkup.

American Cancer Society

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Address

Experience with Cancer of the Stomach and the Colon and Second Look Procedure*

OWEN H. WANGENSTEEN, M.D.
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SOME OF YOU CONTEMPLATING retirement 50 years hence will see many troublesome facets of the current problems of cancer solved. It has been a great privilege to have had the opportunity over many years to participate in the attack upon clinical problems of cancer at the University of Minnesota. I confess, however, to a feeling of real disappointment over our modest accomplishment. The achievement of a 25-percent survival for gastric cancer which I previsioned 20 years ago has not materialized. Yet I feel certain that with more consistent early diagnosis that objective can be achieved and surpassed.

Cancer Detection

Cancer has been one of my keen concerns during my tenure here; yet I recognize that we have all been too long on the wrong side of the cancer woodpile. In March 1948, our Cancer Detection Center came into being after long struggles with the problem in the School and with the Cancer Council of the State Medical Society. It is necessary to cultivate a spirit of patience while trying to persuade others to one's own point of view. Overnight conversion rarely attends such efforts. While still continuing an aggressive approach to late cancers, we began to direct even more attention to finding methods of detecting early cancer. With the cooperation of our colleagues in the Medical School and the State Medical Society we were provided a good opportunity to search for methods of discovering malignant tumors while they were still asymptomatic. A number of my colleagues over the years have contributed importantly to this effort, including Doctors David State, George Moore, Claude Hitchcock, Brannon Hubbard, Albert Sullivan, Donald Shahon, and the present Director of the Cancer Detection Center, Dr. Victor Gilbertsen. The areas in which a telling impact was made were: cancer of the uterine cervix, rectum and breast.

Chemotherapy—A Mixture of Hope and Disappointment

Professor Haddow of England remarked recently that important progress had been made in chemotherapy, especially with two malignancies: chorionepithelioma and Burkitt's lymphoma. To be sure, that is a good beginning; but many people have undoubtedly shed tears of frustration over what seems to be only a modest accomplishment after so much dedicated effort and lavish expenditure.

Alimentary Tract Cancer

My own special concern with cancer relates largely to cancers of the alimentary canal. When I became a member of the Surgical Staff in the middle 20's we had no records of patients with gastric cancer who had survived for more than a year or two after surgery. Total gastrectomy had not been tried, and five-year cures were few indeed in the hands of the best of gastric surgeons.

There are some areas in which there has been little improvement in surgical management of cancer; surgery for cancer of the breast is a case in point. My experience suggests that this is primarily due to the long silent interval during which the cancer is steadily growing without producing symptoms. By the time the patient does come because of symptoms, we are already dealing with a late cancer. We began 20 years ago to gain some information on the length of the silent, asymptomatic interval in mucosal gastric cancers. Paraffin-

*Presented at the Interdepartmental Cancer Seminar, University of Minnesota, June, 1967.

fixed pathological sections of the resected stomach in six such instances indicated that, unlike the optimistic report of the frozen section at operation, we had left residual tumor behind. We did not then have the courage to reoperate upon the patient shortly thereafter. However, we did have the opportunity to assess the length of time intervening until symptoms returned from continued or regrowth of the cancer. The time interval was approximately two years. The experience indicated how long the latent period conventionally is before the cancer produces symptoms. I think that in dealing with any kind of cancer, this is one of the major problems.

Surgical management of cancer of the lung has come during my tenure. Accomplishments in this field are indeed very modest, and there is a compelling need to devise new techniques for determining the presence of lung cancer earlier in its course. Much good will result from the elimination of one of the important causative agents: tobacco smoking. Some are still skeptical of this; but one piece of interesting supporting evidence is found in Iceland, where most of the country is heated by steam and automobiles are few, but smoking and cancer of the lung are both prevalent.

Incidence of Gastric Cancer

When I started my activities here, gastric cancer took a larger toll than any other cancer in the United States. Since 1940, however, mortality from cancer of the large bowel (colon and rectum) has exceeded that of cancer of the stomach. Today more than 40,000 lives a year are lost from this cause alone in our country.

Reports emanating from many areas of the world suggest definitely that the incidence of and the mortality from gastric cancer have been declining steadily for almost two decades. Contrasting the two-year period of 1952 to 1954 with that of 1962 to 1964 a reduction of more than 35 percent in the mortality of gastric cancer has occurred in white male and female patients in the United States registration area.

Precursors of Gastric Cancer

With regard to cancer of the stomach we have little knowledge of its precursors. Concerning the small adenomatous gastric polyps there is some controversy. The feeling of our own group here, especially of Dr. Lyle Hay who has been an ardent student of the problem, is that when these lesions become 2 cm. or more in diameter they should be regarded as probable cancers; in fact, in our experience, 50 percent of lesions of that size were found to be malignant on histological study (Table 1). Such polyps are the only certain precursors of cancer in the stomach and account for perhaps less than 10 percent of all gastric malignant neoplasms. Konjetzny of Hamburg was a keen proponent of gastritis as an antecedent of gastric cancer; and it has been well established that the atrophic gastritis of pernicious anemia predisposes to gastric cancer.

The incidence of gastric cancer has been declining in Iceland where it was formerly very prevalent. The consumption of smoked meats as a possible cause has been a controversial issue. One of my proteges, Professor Snorre Hallgrimson, said it was his impression from a stay in Minnesota that we ate as much smoked food as they did in Iceland. If smoked food were an important factor, with the prevalence of charcoal broilers in almost every householder's backyard, we should see a great increase in cancer of the stomach, instead of the observed marked decrease. Perhaps the ultimate solution will lie in detecting some other important dietary influence.

Environmental Factors of Gastric Cancer

In January 1967 a very interesting paper by Boyland of the Chester Beatty Cancer Institute

TABLE 1
University of Minnesota Experience with Cancer and Gastric Polyps

	Number	Cancer
Single polyps*		
Polyps less than 2 cm in diameter	81	1 = 1.2%
Polyps greater than 2 cm in diameter	14	6 = 42.8%
Multiple polyps†		
Patients with more than 7 polyps	20	7 = 35%
Patients with more than 50 polyps	6	3 = 50%

*Data abstracted from two papers by Hay
†Patient experience for past twenty years

in London implicated bracken, an uncultivated fern and the curse of farmers in the hill country of southwest England and Wales, as a frequent source of cancer of the alimentary tract of cattle. Evans and Mason produced cancer in the alimentary tracts of mice fed on a diet containing dried bracken. This observation suffices to focus renewed interest on ingested carcinogens as an etiologic agent in cancer genesis. The role of such an environmental influence (smoking) is now well established for cancer of the lung and bladder.

The prevalence of gastric cancer may be diminishing because of less ingestion of carcinogens; the other possibility is that the better diet of 1967 provides more protection against ingestion of carcinogens than did the diet of our predecessors of a generation or more ago. Boyland believes that the carcinogen of bracken may diffuse into water supplies and be ingested by man.

Whereas the atrophic gastritis of megaloblastic anemia, as stated earlier, favors the development of gastric cancer, yet today, with effective treatment of patients with pernicious anemia wth vitamin B_{12}, gastric cancer in this condition seems to be far less frequent than before Minot's discovery.

Case Illustrating the Difficulty in Recognizing Mucosal Gastric Cancer

It is pertinent here to refer to a patient I saw with Dr. Leo Rigler about 20 years ago. The patient had come from another hospital complaining of abdominal pain and was told that he had a defect in the pyloric end of the stomach which, on X-ray examination here, was not apparent. My chief responsibility as a gastric consultant over the years in this hospital has been to ask the simple question, "Has your stomach been pumped?" It is astonishing how often this simple procedure is neglected. On aspiration and histamine stimulation, this patient had 8 mEq. of free hydrochloric acid. Because of pain and the low acid value he was again re-evaluated radiologically, but no lesion was found. However, on gastroscopy a lesion the size of one's palm was described by Dr. Ylvisaker on the lesser curvature in the upper gastric fundus. Thereupon Dr. Rigler, who is certainly one of the finest students of gastric roentgenology, carried out a third study and felt there might be something on the lesser curvature. I did not see or feel a lesion at the time of surgery. Mindful of Dr. Ylvisaker's gastroscopic observation I excised all but five to 10 percent of the stomach. One lymph node was involved with malignancy. The patient, a prominent jurist in the area, continues well and active. He owes his life, therefore, to the evacuation of his gastric contents which indicated the necessity for further study. Abdominal pain and achlorhydria point an accusing finger at gastric cancer.

Japanese Clinicians and Gastric Cancer

Japanese radiologists recognize gastric mucosal lesions by the simple expedient of putting 200 ml. of air into the stomach early in the examination. The air separates very nicely from the opaque medium. The examination is performed in bright light. The examiners rotate patients from side to side repeatedly during the fluoroscopic examination and take pictures in various positions. I saw several small lesions identified in this manner. I was at first a bit skeptical concerning the alleged malignancy of such lesions. However, on returning and submitting the beautiful pictures in Professor Kuru's book on gastric malignancy to my pathology colleagues, Drs. Paul Lober and Robert Hebbel, who reaffirmed the validity of the claims of the Japanese pathologists, I am quite prepared to admit that these mucosal lesions detected by Japanese radiologists are bona-fide cancers. Whether the Japanese use X-ray media different from ours I do not know. Every patient suspected of having a gastric lesion in a Japanese clinic is submitted quite routinely to gastroscopy. In a hospital the size of ours there would be perhaps 10 gastroscopists as busily engaged in clinical gastric studies as are the radiologists. Moreover, the gastric camera is also used quite routinely in such assessments.

Japanese clinicians do less well, however, with esophageal cancer. In an informal conference during the session of the 9th International Cancer Conference held in Tokyo in October 1966, Professor Komei Nakayama said that of 3,000 patients operated upon for esophageal cancer by him and his associates,

in only four was cancer limited to the mucosal surface.

University of Minnesota Medical Center Experience with Gastric Cancer

To sum up our experience with gastric cancer: we have had some 1,756 cases from the beginning of our study in 1936 until 1958, comprising the total number seen in the clinics or wards of the University Hospitals. Of that number, we operated on 89 percent and did resections in 80 percent of the patients; but our overall success was very modest. I had previously expressed the hope that before I put my scalpel down we might actually have five-year survivals on the order of 25 percent; but the best we have been able to accomplish is a 17-percent five-year survival, though many of these patients survive for 20 years and more. However, of the patients who came in with local lesions, the five-year survival rate adjusted for age is 55 percent; and in some small series in which the lymph nodes were negative, we had as many as 70-percent five-year survivals (Table 2).

Inasmuch as Japanese clinicians frequently recognize gastric cancer limited to the mucosa or submucosa, their cure rates are considerably better than ours. In fact, reports from Japan suggest that of patients currently undergoing resection of the stomach for gastric cancer, 20 to 25 percent show involvement only of mucosa and submucosa. Japanese surgeons report a survival rate of nearly 100 percent in such cancers. Only by following their diagnostic precepts can we begin to emulate their success with gastric cancer.

The Second-Look Procedure for Gastric Cancer

"Second-look" surgery for cancer of the stomach has been less successful than second-look surgery of the colon. Of our uncured second-look patients with gastric carcinoma, 19 percent were alive at four years; therefore the procedure in these cases did extend life. Even though the second-look procedure produced only eight percent five-year survivors in patients with residual gastric cancer on the first surgical re-entry, it did succeed in prolonging life, even though it failed to cure. Is this not better than telling the patient there is nothing more to be done for him? (Table 4).

Cancer of the Colon

In the surgical management of cancer of the colon, I have been partial to near or total colectomy for cancers distal to the hepatic flexure in standard risk patients since the middle 40's. I recall a patient in 1955 who had undergone two prior excisions for cancer of the colon in another clinic. Two years after the last procedure his physician sent him here. There was a new extensive lesion in the transverse colon. A total colectomy was done, anastomosing the ileum to the rectum. On being

TABLE 2
University of Minnesota Resection Experience with Carcinoma of the Stomach from 1950 through 1958

Treatment	No. of Patients	Five-Year Survival (Age Adjusted)
Localized, resected for cure	110	55%
All cases resected for cure	268	36%
All cases resected	431	22%
All cases	604	17%

TABLE 3
University of Minnesota Operative Experience with Carcinoma of the Colon from 1940 through 1959

Data	No. of Patients	Five-Year Survival (Age Adjusted)
All patients	689	41 8%
All cases resected	453	53 %
Standard curative resections	377	58.6%
Dukes' class A	161	69.6%
Dukes' class B	89	62.9%
Dukes' class C	127	41.7%

TABLE 4
University of Minnesota Experience with Second-Look Procedure with Cancer Present on Re-Entry

Site	No. of Patients	Five-Year Conversions
Stomach	38	3 = 8%
Colon	40	7 = 17%
Ovary	11	2 = 22%
Retroperitoneal sarcoma	10	3 = 30%

informed of the extent of colon removed the patient asked why that was not done in the first instance? The same question bears repetition today. My experience has taught me that all patients operated upon for colon cancer, having less than a near or total colectomy, need annual air contrast barium enema studies. Over a two-year period I saw three patients with a new colic cancer, whose initial operation had been done 13 to 18 years before.

In standard-risk patients, near or total colectomy can be done with operative hazards not far out of line with those incurred in segmental or hemicolectomy. I am partial to the closed method of anastomosis and to an anastomosis between the cecum and the rectum. The alternative is ileoproctostomy with excision of no more than one or 2 cm. of the ileum. We have yet to see a patient with near or total colectomy with persistent diarrhea.

Our best series of consecutive cases of colectomy in this hospital was in the two-year interval of 1941 to 1943 when 61 partial colectomies, employing the closed anastomosis, were performed—with only one hospital death*. Penicillin in very small quantities became available for civilian surgery for the first time only in the summer of 1944. The important desideratum in colon surgery is precise technique with complete avoidance of spillage (Table 3).

The Second-Look Procedure for Cancer of the Colon

Japanese surgeons are more alert to the potentially greater hazards of so-called "Dukes' B" lesions in which penetration of the cancer to the surface occurs. The second-look procedure was first undertaken in this clinic for cancer of the colon in 1948. When I first proposed the procedure to a patient who was found to have an extensive cecal cancer with large clusters of grossly positive lymph nodes in the ileocecal mesentery, the patient asked me, "What evidence have you as to the likely value of such a procedure and what experience have you had?" I admitted that I had had no experience but explained the disparity in accomplishment between lymph-node negative and positive cases. She accepted my suggestion and returned six months later for re-exploration. This patient with an aggressive cecal lesion had six looks before the last re-exploration was negative for residual cancer. When I had the privilege then of telling this courageous lady that there was no residual cancer, she shed a tear; whatever her emotions were, she was too brave to weep outright. She died 12 years later in this hospital of a cerebrovascular accident; no evidence of cancer was found post mortem.

The accompanying chart (Table 4) summarizes our experience with the second-look procedure for cancer of a number of intraperitoneal organs. Three of 10 patients with rhabdomyosarcoma (30 percent) were salvaged and converted to a cancer-free status by second-look operations; 22 percent of 11 patients with cancer of the ovaries were salvaged; for the colon the salvage rate was 17 percent, with eight percent for the stomach.

Patients with Cancer Should Be Told

Obviously patients undergoing second-look procedures should be frankly informed of the nature of their illness. A number of years ago I heard Lowell Thomas say on the radio that Babe Ruth (August Herman), the great hero of baseball, had died of cancer, and that he was very fortunate not to have known that he had the disease. My experience tells me, however, that if you fail to tell a patient, you are doing him a gross injustice. Often when I tell a patient that he has a cancer, he will say, "How glad I am you told me because now I can discuss it with my husband (or wife) who does not know that I know that I have cancer." In other words, if you deceive the patient, he will participate in the deception. Leon Tolstoy wrote very interestingly of this situation in the Death of Ivan Ilych, a brief essay that every medical student should read. It concerns a successful Russian lawyer who probably had cecal cancer. The physician, the patient's wife and his daughter participated in the deception by not telling Ivan the true nature of his illness. They obviously were not yet prepared to face the Gethsemane in another's life. Their daily round of responsibilities and pleasures could not be broken. When is sincerity more appreciated than by a sick person who is too weak to fight back? Husbands will say, "Don't tell my

*Surg 14:403, 1943.

wife she has cancer." However, the physician's greatest responsibility is to his patient. Moreover, from long experience I can tell you it is the wisest policy to tell. One must *never,* of course, extinguish hope.

I was interested in the problem presented earlier today. That patient demonstrated the tenacity with which people hold onto life. I have been told by a few friends that if they were discovered to have cancer, nothing should be done about it. It is amazing how such a person's mind changes when he learns that he actually has cancer. It is then *his* problem; before, it was *only* a philosophic matter. Much of my work has been with geriatric aspects of surgery. In resolving the mode of management of a problem in a patient well along in years in the outpatient clinic, my first question usually is, "How old do you want to live to be?" Answers are uniformly the same: "Well, as long as the weather is fair and the company reasonably good, do what you can to keep my poor craft afloat." Life is still dear to most men in the eighth, ninth, or even tenth decade. Even the suggestion that you are sincerely interested in trying to do something, even in desperate situations, is a source of great hope and inspiration to patients.

Finally, I would like to stress the need for surgeons thinking broadly—beyond the borders of their own field when dealing with cancer. Early detection can pay great dividends, of which there is abundant evidence in cases of cancer of the cervix, with a reduction of mortality of 50 percent (United States figures). Approximately 90 percent of patients with early cancer of the breast detected in our Cancer Detection Center were alive five years later, an achievement far superior to that of patients who come to the hospital with the clinical diagnosis of breast cancer. And similarly with early detection of rectal cancer, as the work of our Cancer Detection Center clearly demonstrates.

If we can rival the accomplishment of Japanese clinicians with gastric cancer and Swedish radiologists in the early detection of cancer of the colon, the young surgeon of today emerging from his years of clinical training will have the opportunity to make a more telling and durable impact upon the problem of visceral cancer than have the surgeons of my generation.

This story serves to reaffirm the interdependence of our professional disciplines. A significant advance in one is reflected in many others. A surgical Rip Van Winkle of today looking in on the activities of his surgical colleagues 50 years hence will be heartened by their greater progress in the field of cancer cure.

We have too long been "Prisoners of hope" in dealing with this disease. Until the pursuit of the nature and causes of cancer eliminates some frequent cancers, cancer detection obviously must be our hope and refuge.

For the privilege of retelling this story, I am grateful.

References

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Anatomy: Remarkably Constant

Gray's Anatomy gives the number of bones in the adult skeleton as follows:

	1887	1959
The spine or vertebral column (sacrum and coccyx included)	26	26
Cranium	8	22
Face	14	
Os hyoides, sternum, ribs	26	26
Upper extremities	64	64
Lower extremities	62	62
Auditory ossicles		6
	200	206



Book Reviews

The proper study of mankind is books.—Aldous Huxley

ANESTHESIA FOR INFANTS AND CHILDREN, by Robert M. Smith, M.D., Anesthesiologist, the Children's Medical Center, Boston, Massachusetts, the C. V. Mosby Company, 1968, Third Edition. 530 pp., 240 illustrations. $17.50.

This third edition of Smith's popular book will contain few surprises for those already familiar with its predecessors. The changes in this edition reflect what has happened in anesthesiology in the past five years. The increasing acceptance of halothane and the enlarging scope of the anesthesiologist's practice outside of the operating room are two examples. But for those unfamiliar with previous editions, those new to the specialty, and even for the many physicians who treat children, the book is highly recommended.

This is first and foremost a very practical book. In it the author describes the problems that are peculiar to pediatric anesthesia and how he and his colleagues have solved them. About one half of the book is devoted to such things as "Anesthesia for Infants Under One Year of Age" (chapter 17; 32 pages) and "Anesthesia for Pediatric Neurosurgery" (chapter 21; 13 pages). These are practical sections with many illustrations and photographs. Midwestern anesthetists will be interested in the enthusiastic advocacy of nonrebreathing techniques, particularly modifications of the Ayre's T-tube, which is not commonly used here.

Dr. Smith knows his subject well and is a most learned and expert physician. However, the success of the book is due at least as much to his power of analysis and exposition, his dry wit and a lucid, simple style, as to his reputation.

Van S. Lawrence, M.D.
Minneapolis, Minnesota

MODERN NUTRITION IN HEALTH AND DISEASE. By Michael G. Wohl and Robert S. Goodhart; Fourth Edition; plus 1240 pp. Lea and Febiger. Philadelphia 1968. $30.00.

This work now in its fourth edition and fifth printing has become a classic textbook in the field of nutrition. There are seventy collaborators. Part I concerns normal nutrition with chapters on body weight, absorption of food, hunger, the usual carbohydrates, proteins, and fats, vitamins, and minerals. Part II is concerned with nutrition in disease. A surprisingly small chapter, less than forty pages, suffices for diabetes mellitus. Part III is an extension of nutrition considering various physiological states such as pregnancy, infancy and geriatrics. A fascinating chapter deals with intoxicating foods, of which there are an extraordinary number sufficient to destroy one's enthusiasm for a ramble in the woods seeking plants, berries, and mushrooms to enhance the daily diet. Most of the chapters are appended with numerous references, many of which deplorably follow the European style, omitting the title. In this country the general opinion is that, next to the names of the authors, the title is the most important part of the article. Modern Nutrition in Health and Disease is recommended as a standard text in the field.

Reuben Berman, M.D.
Minneapolis, Minnesota

MAY YOU LIVE IN HEALTH. By Aaron Friedell, M.D., 69 pages, Minneapolis, Minn.

In Psalms 139:14, David says of himself that he is "fearfully and wonderfully made." So are we all!

Just how fearfully and wonderfully is conveyed by this compact little book wherein Aaron Friedell informs us by text and illustration how precisely and intricately structure and function correlate in the human organism. It is a book for anyone to profit by. For the few of us who have never realized the amazing complexity of man's anatomy and physiology the book is a revelation; for the rest of us a fascinating review.

The figures and diagrams are excellent; they come warm and alive under scrutiny: cells, tissues, organs, systems—each making its own unique contribution in the "pentagon" of optimum health: proper diet, exercise, elimination, breathing, and mental attitude.

Such a book could conceivably be dull; but this one is not. From page one on, the author's clarity of style and sincerity of conviction carry the reader along effortlessly, setting him down at page 69, resolved to eat, breathe, exercise, eliminate, and think *right*. And that, after all, is the main purpose of the book.

Doctors might do well to recommend MAY YOU LIVE IN HEALTH to their patients and to follow its advice themselves.

C.O.R.

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Special Article

A Psychological Field Theory of Adolescence

MARSHALL D. SCHECHTER, M.D.*
Oklahoma City, Oklahoma

ADOLESCENCE IS A period of internal destruction of early parental images and a vigorous drive toward replacement by attachment to new objects. The symptoms seen at this time of life—whether a mild mood change or more intense depressions (including suicides), psychotic withdrawals or antisocial activity—can best be understood as a manifestation of problems surrounding the separation and destruction of internalized primary objects and the finding of suitable new ones. Treatment is aimed at fostering the break with these infantile images and aiding the replacement with satisfactory, stable and worthwhile object ties.

This presentation is an attempt to form a theoretical basis for repeatedly observable clinical phenomena during adolescence. As an introduction, I will describe a brief encounter between a child and his mother to illustrate the conflicts to be anticipated during the process of adolescence.

An argument took place between a preadolescent and his mother. As it grew more heated, the boy decided to run away from home. His mother asked how he would eat. He stated that he would take money from his bank. She asked where he would sleep. This he said was none of her business. She wondered about clothes and keeping warm. He said he'd pack a knapsack. Then his mother said that she was sorry that he felt so angry and that she and his father would be very worried. The boy answered that he would write. His mother asked what he would say. His answer, half in jest, was, "Wish you were here!"

Normality of Process

It is my hypothesis that depressions and mood changes in the adolescent are developmentally normal. The alterations that occur are functionally related to the destruction of the primary infantile tie with the parents (the introjects) or internal images with subsequent periods of mourning and/or its psychic partner by denial, elation. In the adolescent, the destruction is slow, continuous and repetitive as well as explosively sudden, discontinuous, and reparative. It is in the normal that we see mainly the *mood* shifts with generally a preponderance of depressiveness (the blue moods). This is especially noted when the partially lost internal object is not replaced immediately by attachment to another suitable, worthy and valued one. It is during these transient episodes of breaking the parental tie (i.e., the destruction of the introject without substitution) that feelings of worthlessness occur. At the same time, anxiety is increased as the sexual and aggressive drives are not secured by attachment to a steady, acceptable non-punitive individual.

Deviations from Normal

It is in the more severe deviations of the normal or in the overtly pathological that either (1) the objects are not given up at all but are kept inviolate by idealization, or (2) the infantile attachment to parents is so completely withdrawn without replacement that it is necessary to regress to pathological self investments, or (3) the energy is directed toward inappropriate, unrewarding and often sadistic objects. In the cases where the inter-

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nalized parental images (the introjects) remain fixed and unchangeable, the adolescent has a "Peter Pan" look and behavior. His chronological physical development is often belied by a face that looks much younger and by actions that are more naive and immature. These children often have feelings of emptiness or manifest depressions.

In the cases where the infantile attachments to parents are withdrawn completely without replacement, the regression gives the clinical picture of psychosis or a severely regressive psychosomatic disorder. In the cases where the infantile attachments to parents are *almost* entirely withdrawn, the symptomatology is that of depression which might lead to suicide.

In the cases where there is a substitution of improper objects, antisocial behavior results. Anna Freud[2] stated, "Where adolescence is concerned, it seems easier to describe its pathological manifestations than the normal processes. Nevertheless, there are at least two pronouncements which may prove useful for the concept: (1) that adolescence is by its nature an interruption of peaceful growth, and (2) that the upholding of a steady equilibrium during the adolescent process is in itself abnormal."

Conflict Impulses

Edith Jacobson[3] noted that the adolescent has not only to finally relinquish his sexual and hostile wishes; but even his affectionate ties to his parents must be loosened. This, she says, is the cause of his grief reactions. What makes it even harder is the fact that it involves also a definite and final abandonment of his practical and mental dependency on the parents. Speaking of the "inner loss" of the infantile love objects in the adolescent, Jacobson says, "It is significant that within the margin of normal development, adolescents may pass through transient periods of narcissistic retreat to the point of real 'inner' object loss. What is *decisive* is less the brief duration than the reversibility of such states."

Jacobson compares adolescent mood swings to the beginning of a schizophrenic process and relates them to self-centeredness reflecting the floods of instinctual energies which have been liberated but not yet attached to new individuals. She comments upon Anna Freud's[1] remarks about the ego treating the superego (conscience) as though it were a taboo lover. Jacobson says, "This is certainly correct. But we may go even further in our understanding by considering besides that these defensive attitudes of the ego toward the superego are part of the adolescent's desperate struggle for freedom and for independent individuality, and hence an expression of the ego's rebellious refusal to 'submit' or 'admit' to any authority or influence, be it from *without* or from *within*."

Conflict

I think one can see the adolescent's need to reorient himself to new object relations—a need to withdraw energies and thus modify his early object relations, particularly since there is such a heightening of both the sexual and the aggressive drives. We can see in teenagers a struggle to maintain contact with parents, but a fear of closeness. We can see a struggle over their desire to be independent while hating the parents who do not demonstrate an interest in them even if the interest centers about saying "no" to their desires. We can see a struggle to freely discharge sexual tensions even if only through fantasy, while yet attempting to reinforce repressions as the fantasies come too close to involving unresolved oedipal attachments.

It is my belief that the rapid shifts in the adolescent's "crushes" are necessary escapes from primary love objects. When in love, the teen-ager is manic-elated; when out of love, morose-depressed. During periods between loves, the feelings of inner loss are often so intense that the adolescent notes severe feelings of depersonalization. Since other symptoms of psychotic disorder can occur simultaneously, one needs to view the past emotional life of these patients and the tendency toward reversibility of these affective states before reaching the diagnosis of a schizophrenic reaction.

Pathology

Anna Freud[2] noted, "Further pathological developments of this state of affairs are worth watching. The hostility and aggressiveness, which serve as a defense against object love in the beginning, soon become intolerable to the ego, are felt as threat, and are warded off in

their own right. This may happen by projection; in that case the aggression is ascribed to the parents who, consequently, become the adolescent's main oppressors and persecutors. In the clinical picture this appears first as the adolescent's suspiciousness and, when the projections increase, as paranoid behavior.

Conversely, the full hostility and aggression may be turned away from the object and employed inwardly against the self. In these cases, the adolescents display intense depression, tendencies of self-abasement and self-injury, and develop, or even carry out suicidal wishes."

Parent vs. Child

Just a few words about the parents of the children who have gross difficulty through adolescence. It has been my experience that there is certainly a reawakening of the parent's own adolescent struggles. But besides this, many of these parents are primarily depressive individuals themselves, who find separation from their children as hard as separation from their own parents. They often are immature, dependent people who have identified with their children and bound them with many gratifications in the early years but then later expected them to satisfy some of their own needs. There is frequently an increased awareness of conscious and unconscious parental attitudes by the adolescent, who at times reacts to these negative feelings. Sudden lessening of parental esteem has the effect of speeding the destruction of the internalized infantile parent images, often resulting in a furious outbreak of delinquent behavior or violence.

Clinical Material

Acting Out as a Means of Replacing Destroyed Objects

Laura, the oldest child of a prominent professional man, was referred because at age 18 she was twice illegitimately pregnant within a four-month period. Her parents were especially concerned, as they felt she did not care what happened to herself; but, much to their surprise, the girl agreed to treatment rather willingly. She was very defensive at first in the interview situation. When asked what the difficulty was, she reiterated what her parents had said. She also stated that she did not even care if she became pregnant again just so long as she could once more date the boy who first made her pregnant. I said maybe this could be cleared with her parents if she really wanted it after our talks, but perhaps her boy friend might not be so willing.

She asked if all that we discussed was confidential and, when told it was, her masked facies changed to a bitter sadness. She told how she was overwhelmed with guilt; how her mother did not understand and never would understand her, and how her father was too involved with his own affairs to pay any attention to her.

The first boy she was impregnated by still captured her thoughts. His major value was his sureness and certainty in handling details of life. He seemed interested and listened to her if she had problems with her parents or other boys. It was this protectiveness and concern about her that finally led to the seduction. In later hours there were elaborations on this theme of how she needed someone strong to guide her and again hints as to her parents' failing her at some particular point. The guilt she spoke of was not that her peers would find out but rather how painful this all was to her parents. Finally with much hesitation and depression she spoke of learning at age 14 of her father's infidelity. She was told by her mother in front of her father and asked to choose between them if a divorce should take place. It was at this point that she felt her world crumbling. All the confidence she had placed in her father was shaken. With the confrontation, she felt weak and helpless and very much identified with her father whom the mother was berating and degrading incessantly. From this time on she began looking for objects to replace not only the debased father but also a vitriolic unaccepting maternal object.

"Peter Pan Syndrome"

Bill's parents brought him for treatment because of an episode of petty thievery which to them appeared childishly illogical and senseless. He had stolen some film from a grocery store where he was well known and where he had been caught stealing just six months before. Bill, who was 16, had many other symptoms,

which included severe suicidal depressions, no friends, thumb-sucking, learning problems despite a high I.Q. and a persistent acne that resisted all dermatologic treatment. This boy was about as tall as his father but was round-faced and cherubic in appearance. He was weighted with depression and guilt. Each time he closed his eyes, he would relive the entire episode of the stealing and the events that followed in the sheriff's station and at home. Throughout his treatment he would return to this event as it represented an attempt at breaking away from his parents—especially his mother—and the subsequent punishment for his flight into independence. He was able to recognize that through the years not only was each act of independent activity sabotaged by himself, but his parents also made independence unacceptable. His fantasies, as he sucked his thumb, consisted of constant fulfillment of all his wishes by a non-punitive, all-giving mother.

Analysis was subscribed to by the parents on a conscious level. Despite this, shortly after treatment began, they kept making so many remarks about the cost in time and money that after the second month Bill came in and announced his decision to terminate treatment. It was at this time that I pointed out the unconscious motives of his parents who were attempting for their own needs to keep him infantilized. He could see on this occasion that they said one thing and then reacted oppositely.

Shortly after this, despite many complaints from his parents about his lack of friends, when Bill made two appointments with friends after school, his parents insisted on knowing the details of his contacts and objected violently to his being five minutes late for dinner following a meeting with his friends. Throughout treatment these discrepancies were reported. Each time Bill was able to note his parents' unconscious motivations, he was able to draw further from them and closer to the analyst. At the peak of his revolt, his grades hit the lowest point of his life. It was evident that he could not accept the authority of his own ego ideal to accomplish his own goals of being an "A" student. The mere fact that somebody or something (even inside himself) was telling him to study was enough to make him go in the opposite direction.

During these periods of total rejection of the introjects, he would report weird detached depersonalized sensations even to the point of having difficulties remembering the shift system of his car or the route to get back to his home. During the terminal portions of his treatment, his organization was so secure that during the usual arguments with his parents about any of his activities he would remain silently aloof. His acne cleared with only one exacerbation when he became aware of his parents' shifting their dissatisfactions onto his sister and his momentary flareup of anger with them again for their lack of understanding.

Regression and Depression

I saw Don off and on for a period of nine years, starting at age 14. His major symptoms included enuresis, a persistent fantasy of making love to girls by beating them first, and fear of the hostility of other boys. All through his treatment until he was in his 20s, he maintained excellent relationships with his parents which he kept questioning, as he knew the revolt adolescents were supposed to go through.

On completion of college he returned for treatment because of depression, which came on when he was touring Europe and attempted to form a sexual relationship with a woman there and was unable to have an orgasm.

Subsequent treatment revealed a persistent, unconscious, homosexual attachment to his father that was threatened by his attempted heterosexual attachment. His enuresis, beating fantasies and fear of injury from his peers, plus the inability to become independent, could be seen as a need to submit passively to an omnipotent male. With the emergence of his sexual desires, he was faced with the possibility of giving up his attachment to his father; and the act of intercourse and the analytic treatment were seen as the beginning of the demolishment of his father's introject. The depression was partially solved by his going into business with his father and giving up treatment.

Regression to Psychosomatic Disorder

As part of the treatment of an epileptic adolescent, petit-mal and grand-mal attacks could be precipitated almost at will whenever sub-

jects dealing with the loss of object relations were mentioned. For example, even though he would give his epilepsy as his reason for not getting a job, the mechanisms beneath this were the same as we see in a school phobia. He was afraid of loss of contact with his mother and her possible death when he was away. This resulted in panic, as her loss was equivalent to his own annihilation.

Infantile Ties with Parents

Kathy was 15 when I first saw her. Her major symptoms were depression and obesity. Treatment was recommended but not continued after the diagnostic workup. Eight months later she was again seen—three months pregnant. The depression was still present but there was an air of satisfaction and elation as she told me that her father was going to arrange for her confinement. The next day the gloating was gone, however. Her father had failed her. The depressed reaction was intense. I arranged placement and saw her through the pregnancy and for a year afterward.

Briefly this was the history: She was the only child of parents who were divorced when she was three years old. She was intensely in love with her father at the time of the separation. Whereas the father remarried and had children with his second wife, her mother did not remarry but continued weekly visits with the patient to her father's house to keep up "friendly relations." When together the father seemed interested and concerned; however, he never made any visits to the child or any arrangements to have her with him.

After puberty, her father became very curious as to her relationships with boys. She confided in him, as she felt her mother really wasn't interested. At the first sign of actual sexual involvement, the father made Kathy promise that she would not indulge unless and until he himself initiated her. She loved him a great deal and felt that she probably would really be acceptable if she showed him she was the best "lay" he ever had. Sexual relations began and continued along with other completely casual ones with pickups at bars. There was even some question as to whether her father was the father of her child. No matter how flagrantly he ignored her, she still cherished the fantasy that he was interested and loved her.

During the entire confinement and the year afterward he made no attempt to contact her. Nevertheless, each Christmas and birthday she considered giving him an expensive gift which she could ill afford. Whenever she was confronted with his lack of interest, she became depressed to suicidal proportions. At these times she would try to elicit signs of her mother's interest but always failed.

Her acting out with men became clear; it was not only an attempt to get the father image she fantasied but also hopefully to have her mother demonstrate an interest by insisting she stop her sexual escapades. Her mother's lack of firmness increased her anxiety, as it drove her again and again to try to find satisfaction from imaginary father figures. She begged for an authoritative figure who could control her impulsive sexual activity and her eating. Not only was her father of no help in supporting superego formation; but when Kathy finally decided to diet, her mother for the first time in years began baking and bringing home pastries and ice cream.

In treatment, Kathy focused all of her longing for a consistent object on me, her analyst, and felt good when she was not allowed to act out without criticism from me. Before each turn to me, there characteristically had to be an episode of disappointment with her parents, a depression, an acting out and then finally an accepting of me as a new, more stable object.

She graduated from high school, and her weight continued diminishing. After this she entered college and worked, all in a city quite distant from her mother and her father.

Parental Roles

There are many times when the treatment program of adolescents is interfered with by the problems of their parents. This could be seen in the case of Bill and Kathy, as well as in the case of Shirley who at 17 was referred because of two abortive suicidal attempts. Shirley was a well-developed, attractive but surly-looking girl who could only talk about her potential successes with boys, her potential

successes in an acting career and her potential successes in her academic work. In actuality, boys took her out only because of what they "could get from her;" drama teachers turned her down repeatedly as she would not take directions, and she had failed one semester and was on her way to another failure because of non-attendance in high school.

Besides these shortcomings, Shirley, who was an only child, would engage periodically in violent physical and verbal battles with her mother, Shirley threatening to kill and her mother threatening to call the police, while her father remained passively unconcerned. This was the picture when I was first consulted.

After a short period during which Shirley blamed everybody and everything for her derelictions, she finally decided that to achieve in any sphere would require some action by herself. I was able to show her how inconsistent her parents had been. For instance, when a punishment was given, it almost immediately was rescinded despite Shirley's partial insistence on fulfilling it. Or, despite her mother's conscious desire for Shirley to go to school, she would sanction any excuse to allow her child to remain at home. The more Shirley saw of these tendencies in her parents, the more distant but simultaneously the more depressed she became. Concurrent with mood shifts in treatment, her mother became more openly provocative and seductive, constantly precipitating fights and then offering unusual rewards during the making-up periods. I received many calls from the mother, complaining about how badly things were going with Shirley. But in spite of these complaints, the mother constantly took the blame on herself, saying she knew she deserved this treatment and realized that she should not have done or said something that precipitated the new fight —but she "just couldn't help it."

Finally, when Shirley spoke of her mother's tendency to incite arguments on the flimsiest of excuses, I suggested that perhaps it would be best for her to say that she did not want to fight and to isolate herself in her room. Three hours after this recommendation, which Shirley acted upon, I received the most blistering denunciation from the mother. For the first time, I was accused of trying to take her daughter away from her and she was "not going to allow it." Treatment was interrupted shortly after this because of supposedly sudden and unusual financial problems.

Destruction and Replacement of Parental Images

Janet, the adolescent daughter of a friend, came home one day and announced that she felt depressed. When questioned by her mother, no difficulties could be discovered either in her academic or in her extracurricular affairs. She isolated herself for the rest of the evening until bedtime. When she came to say goodnight to her mother, Janet led the conversation around to marriage—the interpersonal as well as the sexual relationships in it. With much dramatic inflection, she announced it was all very disgusting. She questioned and verbally abused her mother who considered love still beautiful and exciting even at her age. Finally, when her mother despaired of her ever retiring that evening or ever having a happy relationship with a man at any time in the future, Janet announced with glee that she had a date the very next night with the handsomest boy in her class. The depression evident at the beginning of the conversation was over at its end. When her mother commented on it the next day, the rapid shift in mood was denied by Janet saying, "Oh Mom, stop always having to be so psychological!"

Discussion

We constantly see the pull toward group formation and of mores irrespective of parental attitude. When the adolescent is not part of the group or when one close friend seems to be more interested in another chum or when a favorite teacher criticizes, sudden depressions occur. In the normal teenager disappointments are often ignored or even welcomed, as they provide another excuse to justify separation from parents. The charge continually made is, "You don't understand" or "Things are different nowadays." What this stands for is, "I won't talk to you or reveal my secrets, as I might enjoy having my dependency needs met and might again be tempted into a child-like relationship with you."

Adult Perspective

It is these intrapsychic phenomena that I believe suggest an answer to a question that many analysts have raised. One of them has stated[2], ". . . . . I am impressed how seldom in the treatment of my adult cases I succeed in reviving their adolescent experiences in full force . . . what we fail to recover, as a rule, is the atmosphere in which the adolescent lives, his anxieties, the height of elation or the depth of despair, the quickly rising enthusiasms, the utter hopelessness, the burning—or at other times sterile—intellectual and philosophical preoccupations, the yearning for freedom, the sense of loneliness, the feeling of oppression by the parents, the impotent rages or active hates directed at the adult world, the erotic crushes —whether homosexually or heterosexually directed—the suicidal fantasies, etc. These are elusive mood swings, difficult to revive, which, unlike the affective states of infancy and early childhood, seem disinclined to re-emerge and be relived in connection with the person of the analyst."

Adults have reported their adolescence: "drifting," "vague," "eerie," "unattached," "alone and apart," "looking for somebody or something to belong to," "unreal," "nobody understood what I thought, felt or did," "isolated."

The adolescents I have seen who have not been able to tolerate real separation from their primary love objects—in other words those adolescents who have not gone through a "revolting" period—maintain the symptomatology of early and middle childhood. It is therefore my contention that the adults who do not recall their adolescence with sharp definity fail to do so because the recollections are highly charged with violent disruptive and destructive affects.

The period of adolescence is a period of destruction of primary object ties and a vigorous drive toward replacement by attachment to new objects. The symptoms seen at this time of life—whether a mild mood change, the more intense depressions (including suicides), psychotic withdrawals or antisocial activity—can best be understood as a manifestation of problems surrounding the separation and destruction of internal primary objects and finding suitable new ones. Treatment is aimed at fostering the break with the infantile attachment to parents and aiding in the substitution of satisfactory, stable and worthwhile object ties.

References

1. Freud, A.: The Ego and Mechanisms of Defense New York: International Universities Press, 1946.
2. Freud, A.: Adolescence, The Psychoanalytic Study of the Child, Vol. XIII, International Universities Press, 1958.
3. Jacobson, E.: Adolescent Moods and the Remodeling of Psychic Structures in Adolescence, The Psychoanalytic Study of the Child, Vol. XVI, International Universities Press, 1961.

Minnesota Medicine Cover Photographs

In order to encourage more physicians to submit color slides for use on the cover of MINNESOTA MEDICINE the competition is being discontinued. The picture editor now invites all physician-photographers to send 35 mm. color slides of suitable subjects for consideration as cover pictures. The format must be horizontal because of printing limitations. Pictures high-lighting Minnesota seasons, places, and activities will have an automatic advantage. No limit as to the number of slides sent will be set, but all slides should be individually identified. All slides will be returned. Physicians whose pictures are used as covers will be recognized in MINNESOTA MEDICINE. We can use many more pictures than we have received in the past.

We Waited in that Office

After waiting hours in a crowded doctor's office, one patient stood up to go. He said, "Well, I guess I'll just go home and die a natural death."

What passes for woman's intuition is often nothing more than man's transparency.—George Jean Nathan

What's New?

Morton Salt Company ("it never rains but, etc.") announces a salt substitute called Half/Salt Mixture. Half/Salt consists primarily of equal parts of sodium chloride and potassium chloride and may be applicable to patients on a restricted sodium intake. The mixture also contains calcium polysilicate, dextrose and 0.01% potassium iodide. The manufacturer claims this mixture overcomes the traditionally bitter and unpalatable sodium substitute taste. This preparation is packaged in a disposable 3½ ounce table salter, now being test marketed.

A new otoscope examining system, for use in the office, has been announced by **Smith Kline & French Laboratories.** The Hotchkiss otoscope will be marketed by the SK&F representatives throughout Canada and the world. The otoscope, designed for one hand operation, eliminates the parallax error, provides greater illumination and is adaptable to photographic recording.

Hong Kong Flu Vaccine "Crash Program" at Parke-Davis Requires 64,000 Fertile Eggs Per Day

Parke, Davis & Company is operating a "crash program" to produce large quantities of vaccine to help protect the American people from an epidemic of Hong Kong influenza which medical authorities expect this winter. "We have to produce the vaccine under scientifically-controlled production and testing methods—all of which take time—but we are confident we can have a safe, potent vaccine ready by early December.

Agricultural Pioneers

Doctors were frequently agricultural pioneers. Dr. George A. Kenny determined to raise apples on his ranch seventeen miles from Salmon, Idaho. Everybody knew that the country was too high and cold for apples, everybody but Dr. Kenny who sent east for Siberian crab-apple trees. He raised wagonloads of apples and made a tangy cider which was popular at ranch parties. His apple trees are still bearing. Dr. Kenny also started a dairy, and when his cows produced a surplus of butter, he put it up in tin cans.

"Doc thinks you can preserve butter like beans," folks said.

That winter when cream production almost ceased, he opened up his tins and sold fresh butter at the trading post at Salmon.

Dr. Guillermo B. Osbourn brought roses, vines, and fruit trees from Rochester, New York, to Southern California in 1855. Soon he was shipping grapes to the East. Twenty years later Dr. John L. Dryer of Soloma made a more significant contribution to California's future as the nation's fruit bowl. He was the first to smudge a citrus grove to head off frost damage.*

*Richard Dunlop: Doctors of the American Frontier, 1965.



Meetings and Announcements

Every addition to true knowledge is an addition to human power.—Horace Mann

DECEMBER

Nicollet-LeSueur County Medical Society, Christmas auction for AMA-ERF Fund, 6:30 p.m., December 2, Dinner, Holiday House, St. Peter.

Southwestern Minnesota Medical Society, Worthington, 7:00 p.m., December 2.

Minnesota Obstetric & Gynecological Society, North Memorial Hospital Auditorium, Minneapolis, 9:00 p.m., December 7.

Camp Release District Medical Society, Hunt Hotel, Montevideo, 7:30 p.m., December 12.

St. Louis County Medical Society, St. Mary's Hospital, Executive Meeting at 6:00 p.m., December 12.

Minnesota Academy of Ophthalmology & Otolaryngology, University of Minnesota, 9:00 p.m., December 13.

St. Louis County Medical Society, Annual Banquet, Kitchi-Gammi Club, 7:30 p.m., December 14.

Renville-Redwood County Medical Society, Redwood Falls Golf Club, 7:00 p.m., December 17.

Freeborn County Medical Society, Annual Meeting and Election of Officers, Dinner, December 19, 6:30 p.m., Albert Lea.

Kandiyohi-Swift-Meeker County Medical Society, Westwood Inn, Spicer, 7:00 p.m., December 19.

Scott-Carver County Medical Society, Ladies Auxiliary Dinner Dance, time and place to be announced.

Waseca County Medical Society, Regular Meeting, December 30.

Symposia on Transplantation-RES Relationships and on RE Aspects of Invertebrate Pathology, Hotel Americana, New York, December 1.

Radiological Society of North America, Inc., Palmer House, Chicago, December 1.

American Society of Therapeutic Radiologists, Palmer House, Chicago, December 3.

American Rheumatism Association, Regency-Hyatt Hotel, Atlanta, December 5.

American Academy of Dermatology, Palmer House, Chicago, December 7.

American Academy of Cerebral Palsy, Americana Hotel, Bal Harbour, Florida, December 10.

Nebraska State Obstetric and Gynecologic Society, New Frontier Hotel, Las Vegas, Nevada, December 5-7. Sec: W. Rumbolz, M.D., 410 S. Saddle Creek Rd., Omaha.

Thirty-Second Annual Meeting
The New Orleans Graduate Medical Assembly

The thirty-second annual meeting of The New Orleans Graduate Medical Assembly will be held March 10, 11, 12, 13, 1969, headquarters at The Roosevelt Hotel.

Nineteen outstanding guest speakers will participate and their presentations will be of interest to both specialists and general practitioners. The program will include fifty informative discussions on many topics of current medical interest, in addition to a clinicopathologic conference, medical motion pictures, round-table luncheons, and technical exhibits. This program is acceptable for three and one-half (3½) prescribed hours and twenty-eight (28) elective hours by the American Academy of General Practice.

An interesting and enjoyable program of entertainment for visiting ladies has been planned.

A Program of Clinical Experience in Outpatient Education for Control of Diabetes Mellitus

The Diabetes Detection and Education Center, 916 East 15th Street, Minneapolis, Minnesota, has developed a program of medical and paramedical education for physicians, nurses, public health personnel, and dietitians. Classes are scheduled for the weeks of: December 2, December 16, and December 30. Rooms and meals are available at the Center at minimum cost.

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the few
who are rich."

John F. Kennedy, Inaugural Address

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WANTED: General practitioner to join two young general practitioners in well-established practice in suburban St. Paul. Excellent office space with lab, x-ray, and emergency room. Salary negotiable, with an association leading to early partnership opportunity. Write MINNESOTA MEDICINE 412, 375 Jackson St., St. Paul 55101.

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He has been a doctor a year now and has had two patients—no, three, I think—yes, it was three; I attended their funerals.—Mark Twain

Minnesota Medicine at a Glance

Cutaneous Clues to Visceral Cancer—*Perry et al.* Page 1719

This paper emphasizes the association with neoplasia of several cutaneous diseases and syndromes. In the disorders presented, the skin findings should alert the physician to the possibility of an associated internal cancer.

Cryptococcosis Presenting as an Osteolytic Rib Lesion—*Kuaity and Lewis* Page 1727

A 46-year-old negro woman, diagnosed as having sarcoidosis 10 years previously, entered the hospital because of evidence of rib destruction on x-ray. Sputum cultures and cultures from the excised rib grew out cryptococcosis neoformans. Treatment with Amphotericin B led to x-ray improvement.

Multiple Endocrine Adenomatosis—*Delaney and Jacobson* Page 1731

A 59-year-old white female with a history of recurrent ulcer required gastric surgery on two occasions. A pancreatic islet cell tumor was found at the last surgical procedure.

Recurrent ulcer prompted investigation of calcium metabolism.

In June 1966, parathyroids were explored and diffuse hyperplasia noted.

The case falls into a category of multiple endocrine adenomatosis.

The author discusses this fascinating syndrome.

Blood Gas Monitoring—*Dines et al.* Page 1735

The purpose of this paper is to review problems in the interpretation and significance of the data obtained during monitoring of patients in respiratory failure. A brief review of the physiology of respiratory acidosis is presented, followed by a discussion of the derangements in man. Seven clinical illustrations are presented to demonstrate some of the problems in the blood gas monitoring of the patient in respiratory failure.

Oliver Wendell Holmes

To The Young Practitioner

You cannot and need not expect to disturb the public in the possession of its medical superstitions. A man's ignorance is as much his private property, and as precious in his own eyes, as his family Bible. You have only to open your own Bible at the ninth chapter of St. John's Gospel,* and you will find that the logic of a restored patient was very simple then, as it is now, and very hard to deal with. . . . Lord Bacon, Robert Boyle, Bishop Berkeley, all put their faith in panaceas which we would laugh to scorn. They had seen people get well after using them. Are we any wiser than those great men?

*This was an occasion in which Jesus anointed the eyes of a blind man. "He went his way therefore, and washed and came seeing."

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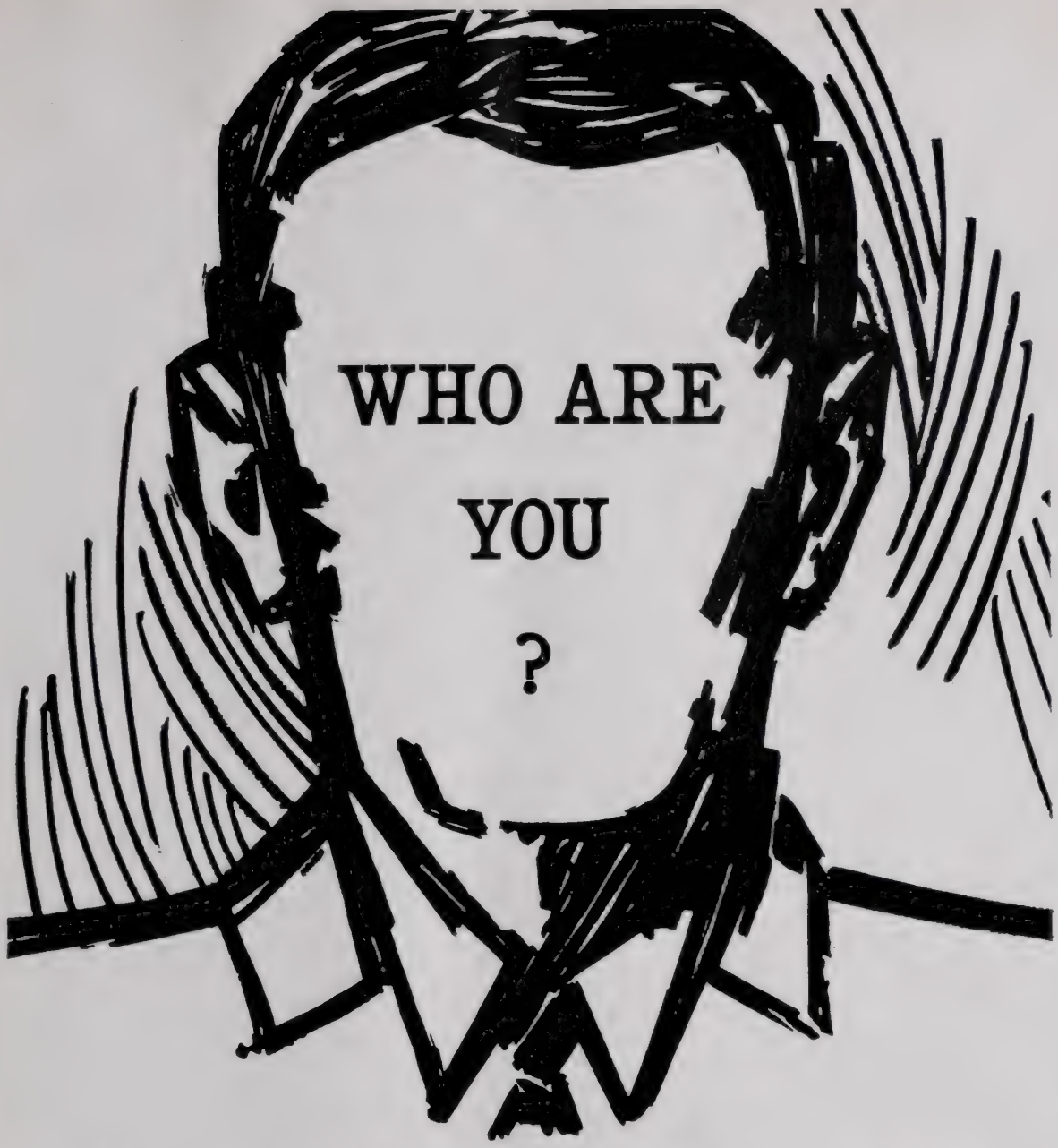
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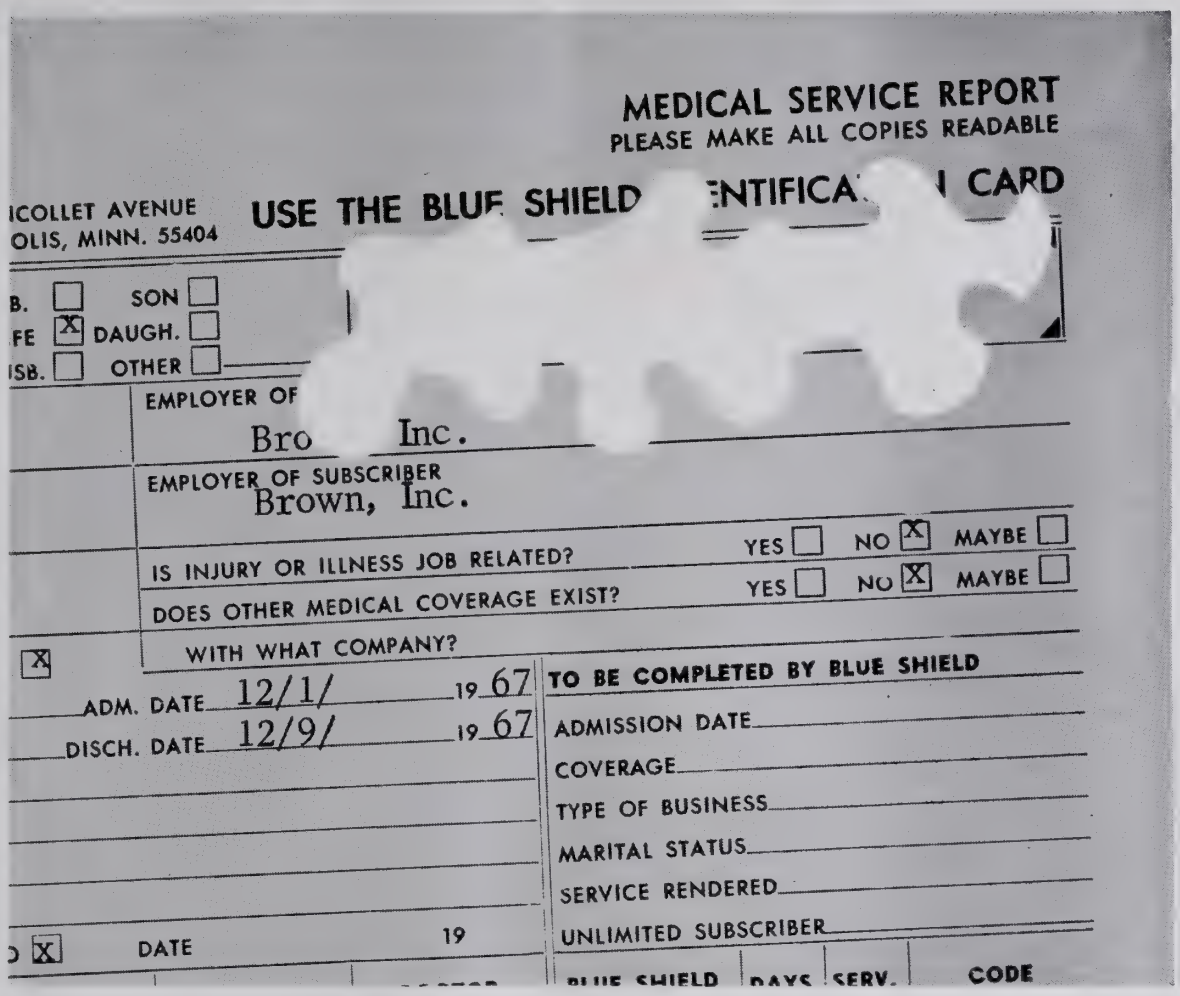
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Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms have occurred following abrupt discontinuance. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation, have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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